Differential expression of key CmPn members distinguishes

histological and immune subtypes of hepatic cancers

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Legends

Suppl. Figures

Suppl. Figure S1. Differentially expressed genes across immune subtypes for Hepatocellular Carcinoma (HCC). A) *Comparisons between wound healing (C1) and IFN-γ dominant (C2) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of differentially expressed genes (DEGs). Results of the gene ontology enrichment analysis comparing C1 and C2 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **B)** *Comparisons between wound healing (C1) and inflammatory (C3) subtypes*. Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of the gene ontology enrichment analysis comparing C1 and C3 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **C)** *Comparisons between wound healing (C1) and lymphocyte depleted (C4) subtypes*. Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of the gene ontology enrichment analysis comparing C1 and C4 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **D)** *Comparisons between IFN-γ dominant (C2) and inflammatory (C3) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of the gene ontology enrichment analysis comparing C2 and C3 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **E)** *Comparisons between IFN-γ dominant (C2) and lymphocyte depleted (C4) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of the gene ontology enrichment analysis comparing C2 and C4 are provided for biological processes (lower left panel), molecular functions

(upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **F)** *Comparisons between inflammatory (C3) and lymphocyte depleted (C4) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of the gene ontology enrichment analysis comparing C3 and C4 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). For all panels, scatter plots display the log2-fold changes and statistical significance of each gene calculated by performing a differential gene expression analysis. Genes in volcano plots with logFC>1.5 and p-value<0.05 are in red while genes with logFC<-1.5 and p-value<0.05 are in blue. All enrichment analysis results were generated using Enrichr where the x axis indicates the -log10(P-value); the top 15 pathways are provided and color-coded (red-up/blue-down) and pathways with p-values<0.05 and FDR<0.1 are bolded.

Suppl. Figure S2. Differentially expressed genes across immune subtypes for Cholangiocarcinoma (CCA). A) *Comparisons between wound healing (C1) and IFN-γ dominant (C2) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of differentially expressed genes (DEGs). Results of the gene ontology enrichment analysis comparing C1 and C2 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **B)** *Comparisons between wound healing (C1) and inflammatory (C3) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of the gene ontology enrichment analysis comparing C1 and C3 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **C)** *Comparisons between wound healing (C1) and lymphocyte depleted (C4) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of

the gene ontology enrichment analysis comparing C1 and C4 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **D)** *Comparisons between IFN-γ dominant (C2) and inflammatory (C3) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of the gene ontology enrichment analysis comparing C2 and C3 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **E)** *Comparisons between IFN-γ dominant (C2) and lymphocyte depleted (C4) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of the gene ontology enrichment analysis comparing C2 and C4 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). **F)** *Comparisons between inflammatory (C3) and lymphocyte depleted (C4) subtypes.* Sample size is shown for each comparing group (top left panel) along with a scatter plot (middle left panel) of DEGs. Results of the gene ontology enrichment analysis comparing C3 and C4 are provided for biological processes (lower left panel), molecular functions (upper right panel), reactome pathways (middle right panel), and KEGG pathways (lower right panel). For all panels, scatter plots display the log2-fold changes and statistical significance of each gene calculated by performing a differential gene expression analysis. Genes in volcano plots with logFC>1.5 and p-value<0.05 are in red while genes with logFC<-1.5 and p-value<0.05 are in blue. All enrichment analysis results were generated using Enrichr where the x axis indicates the -log10(P-value); the top 15 pathways are provided and color-coded (red-up/blue-down) and pathways with p-values<0.05 and FDR<0.1 are bolded.

Suppl. Figure S3. RNAseq expression profiling for key CmPn players integrating sociological, follow-up, and clinical survival data for hepatic cancers: We investigated key CSC, mPRs and nPRs (CmPn) players expression analysis (along with established liver cancer biomarker *AFP*) using demographic and follow-up

data to assess differential expression across major races and evaluate impact on tumor recurrence following treatment. **A)** Differential expression for key CmPn members, along with *AFP,* among the three most prevalent races diagnosed with CCAs (n=45). **B)** Differential expression for key CmPn members, along with *AFP,* among the five major locations for tumor recurrence in patients diagnosed with CCAs (n=20). **C)** Differential expression for key CmPn members, along with *AFP,* based on vital status for patients diagnosed with CCAs (n=45). **D1-2)** Differential expression of key CmPn members, along with *AFP,* for patients diagnosed with HCC (**D-1,** n=412) or patients diagnosed with CCAs (**D-2,** n=45). **E1-2)** Differential expression for key CmPn members, along with *AFP,* for residual tumor classification in patients diagnosed with HCCs (**E-1,** n=380) or for patients diagnosed with CCAs (**E-2,** n=41). For all graphs, X axis details genes profiled, while Y axis details Log2 batch effects normalized RNAseq expression data. All graphs were produced using the Xena platform.

Suppl. Figure S4. Hematoxylin and Eosin (H&E) imaging of microarray slides for normal and seven subtypes of hepatic cancers. H&E pre-stained microarray slides were purchased to visualize tissue patterns and subcellular structural differences between lesion subtypes. A representative normal healthy liver tissue (NORM) is displayed (Panel A) along with a representative hepatocellular carcinoma (HCC) tissue (panel B), cholangiocarcinoma (CCA) tissue (panel C), combined hepatocholangiocarcinoma (cHCC-CCA) tissue (panel D), adenosquamous carcinoma (ASC) tissue (panel E), undifferentiated pleomorphic sarcoma (UPS) tissue (panel F), clear cell carcinoma (CCC) tissue (panel G) and hepatic angiosarcoma (HAS) tissue (panel H). Tissues were imaged using a Nikon EclipseTi microscope with Images acquired using a 20X objective lens to ensure coverage of tissue.

Suppl. Figure S5. Immunofluorescence imaging of AFP and nPRs for hepatic cancers. Comparative protein expression patterns for AFP and nPRs were measured with immunofluorescence-labeled antibodies,

normalized against nuclear staining (DAPI), and quantified using Nikon Elements Analysis software. **A)** Representative IF images of AFP protein expression between NORM and CCA tissues is displayed, along with **n**ormalized quantification for all images. **B)** Normalized quantification for all images of nPRs protein expression among different liver cancer types and NORM tissue (images not shown).

Suppl. Tables

Suppl. Table S1. Databases used for NCI-GDC clinical profiling of hepatic cancers in Figure 1. Databases used by the Genomic Data Commons (GDC) data portal from the National Cancer Institute (NCI), are detailed in tab 1 for the general analysis of hepatic cancers without any gene filters (general clinical observations) or tab 2 for the filtered analysis to only analyze patient samples with differential expression for any of the key CmPn players (CmPn network associated clinical observations). The database of Genotypes and Phenotypes (dbGaP) study accession number is provided for each database.

Suppl. Table S2A. Raw RNAseq/enrichment results for normal healthy patients compared to HCC patients. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Figure 2C-1 is provided in tab 1 with gene symbol in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding KEGG pathways enrichment analysis performed using Enrichr is provided in tab 4. For Tabs 2-4, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up-regulated), respectively, or columns I-N (down-regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are

color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S2B. Raw RNAseq/enrichment results for normal healthy patients compared to CCA patients. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Figure 2D-1 is provided in tab 1 with gene symbol in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding KEGG pathways enrichment analysis performed using Enrichr is provided in tab 4. For Tabs 2-4, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up-regulated), respectively, or columns I-N (down-regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S2C. Raw RNAseq/enrichment results for HCC compared to CCA patients. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Figure 2E-1 is provided in tab 1 with gene symbol in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding KEGG pathways enrichment analysis performed using Enrichr is provided in tab 4. For Tabs 2-4, the terms, p-value, FDR, Z-score, combined score and corresponding genes are

provided in columns A-F (up-regulated), respectively, or columns I-N (down-regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S3. Antibodies and Microarray slides used for Immunofluorescence / H&E analysis. Details regarding application, antigen, gene, clone, manufacturer, catalog number, and primary and secondary dilutions (if applicable) for primary and secondary antibodies used are listed in tab 1. Information about microarray slides purchased for imaging are detailed in tab 2 with catalog #, details, manufacturer, and application. Abbreviations: IF, immunofluorescence; IHC, immunohistochemistry.

Suppl. Table S4A. Raw RNAseq/enrichment results for HCC Immune subtypes C1 v C2. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 1A is provided in tab 1; gene symbol is in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-values in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up-regulated), respectively, or columns I-N (down-regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S4B. Raw RNAseq/enrichment results for HCC Immune subtypes C1 v C3. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 1B is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S4C. Raw RNAseq/enrichment results for HCC Immune subtypes C1 v C4. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 1C is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which

are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S4D. Raw RNAseq/enrichment results for HCC Immune subtypes C2 v C3. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 1D is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S4E. Raw RNAseq/enrichment results for HCC Immune subtypes C2 v C4. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 1E is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs

2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S4F. Raw RNAseq/enrichment results for HCC Immune subtypes C3 v C4. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 1F is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S5A. Raw RNAseq/enrichment results for CCA Immune subtypes C1 v C2. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 2A is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-values in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular

functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up-regulated), respectively, or columns I-N (down-regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S5B. Raw RNAseq/enrichment results for CCA Immune subtypes C1 v C3. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 2B is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S5C. Raw RNAseq/enrichment results for CCA Immune subtypes C1 v C4. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 2C is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column

E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S5D. Raw RNAseq/enrichment results for CCA Immune subtypes C2 v C3. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 2D is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S5E. Raw RNAseq/enrichment results for CCA Immune subtypes C2 v C4. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with

CmPn expression differences) in Suppl. Fig 2E is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

Suppl. Table S5F. Raw RNAseq/enrichment results for CCA Immune subtypes C3 v C4. The raw RNAseq data used to generate the differential expression analysis (volcano plot and corresponding table with CmPn expression differences) in Suppl. Fig 2F is provided in tab 1; gene symbol is located in column A, log fold changes (logFC) in column B, average expression in column C, t-values in column D, P-value in column E and adjusted P-values in column F. The raw data for the corresponding Gene Ontology enrichment analysis performed using Enrichr is provided in tab 2 (Biological processes) and tab 3 (Molecular functions). The raw data for the corresponding signaling pathways enrichment analysis performed using Enrichr is provided in tab 4 (reactome signaling pathways) and tab 5 (KEGG signaling pathways). For tabs 2-5, the terms, p-value, FDR, Z-score, combined score and corresponding genes are provided in columns A-F (up regulated), respectively, or columns I-N (down regulated), respectively. The top 15 terms (which are illustrated in the corresponding figure) are color-coded (red for up regulated or blue for down regulated) and terms that had p-values <0.05 and FDR<0.1 are bolded.

S1A

Immunological Subtypes	Sample size
Wound Healing (C1)	22
IFN-γ dominant (C2)	45

Down-regulated in Wound_Healing_Immune_C1_   **Up-regulated in Wound_Healing_Immune_C1_**

(Volcano plot: y-axis -log10P from 0 to 16, x-axis log2FC from -4 to 4)
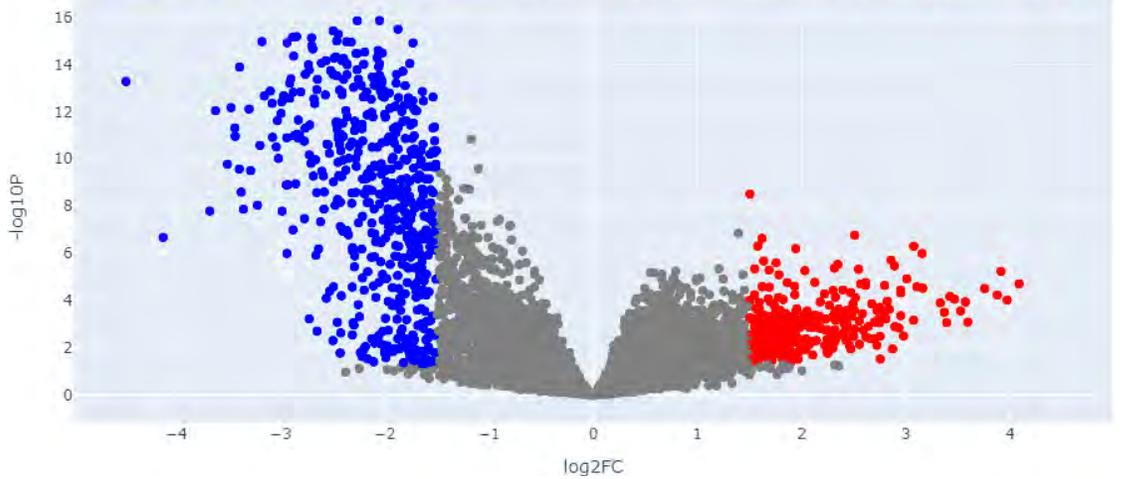
Gene symbol	logFC	AveExpr	t	P.Value
CCM1	0.518192	3.930383	3.14197	2.00E-03
PAQR6	0.68546	1.056312	2.055773	4.00E-02

Molecular Functions

*Up-regulated in Wound_Healing_Immune_C1_*

- DNA binding (GO:0003677)
- myosin binding (GO:0017022)
- myosin V binding (GO:0031489)
- calcium-dependent phospholipid binding (GO:0005544)
- coreceptor activity involved in Wnt signaling pathway, planar cell polarity pat
- R-SMAD binding (GO:0070412)
- DEAD/H-box RNA helicase binding (GO:0017151)
- protein binding involved in heterotypic cell-cell adhesion (GO:0086080)
- mitogen-activated protein kinase binding (GO:0051019)
- coreceptor activity involved in Wnt signaling pathway (GO:0071936)
- bicarbonate transmembrane transporter activity (GO:0015106)
- Wnt-activated receptor activity (GO:0042813)
- protein kinase C binding (GO:0005080)
- transmembrane receptor protein kinase activity (GO:0019199)
- cytoskeletal adaptor activity (GO:0008093)

(x-axis -log10P: 0, 0.5, 1, 1.5, 2, 2.5)

*Down-regulated in Wound_Healing_Immune_C1_*

- *MHC protein binding (GO:0042287)
- *MHC protein complex binding (GO:0023023)
- *cytokine receptor activity (GO:0004896)
- *MHC class II protein complex binding (GO:0023026)
- *MHC class I protein binding (GO:0042288)
- *chemokine receptor binding (GO:0042379)
- *MHC class II receptor activity (GO:0032395)
- *T cell receptor binding (GO:0042608)
- *chemokine activity (GO:0008009)
- *CCR chemokine receptor binding (GO:0048020)
- *phosphatidylinositol-3,4-bisphosphate binding (GO:0043325)
- *MHC class II protein binding (GO:0042289)
- *chemokine receptor activity (GO:0004950)
- *non-membrane spanning protein tyrosine kinase activity (GO:0004
- *G-protein coupled chemoattractant receptor activity (GO:0001637)

(x-axis -log10P: 0, 2, 4, 6, 8, 10, 12)

Reactome pathways

*Up-regulated in Wound_Healing_Immune_C1_*

- *Non-integrin membrane-ECM interactions Homo sapiens R-HSA-300
- *Laminin interactions Homo sapiens R-HSA-3000157
- Signaling by Robo receptor Homo sapiens R-HSA-376176
- ECM proteoglycans Homo sapiens R-HSA-3000178
- Rho GTPase cycle Homo sapiens R-HSA-194840
- Regulation of gene expression in late stage (branching morphogenesis) panc
- Cell-Cell communication Homo sapiens R-HSA-1500931
- p75 NTR receptor-mediated signalling Homo sapiens R-HSA-193704
- Cell death signalling via NRAGE, NRIF and NADE Homo sapiens R-HSA-2049
- Signaling by BMP Homo sapiens R-HSA-201451
- Type I hemidesmosome assembly Homo sapiens R-HSA-446107
- RHO GTPases Activate Rhotekin and Rhophilins Homo sapiens R-HSA-5666
- Cell junction organization Homo sapiens R-HSA-446728
- Signaling by Rho GTPases Homo sapiens R-HSA-194315
- Neurotoxicity of clostridium toxins Homo sapiens R-HSA-168799

(x-axis -log10P: 0, 1, 2, 3, 4)

*Down-regulated in Wound_Healing_Immune_C1_*

- *Immune System Homo sapiens R-HSA-168256
- *Adaptive Immune System Homo sapiens R-HSA-1280218
- *Immunoregulatory interactions between a Lymphoid and a non-Lym
- *Cytokine Signaling in Immune system Homo sapiens R-HSA-12802
- *Interferon Signaling Homo sapiens R-HSA-913531
- *Interferon gamma signaling Homo sapiens R-HSA-877300
- *Innate Immune System Homo sapiens R-HSA-168249
- *Generation of second messenger molecules Homo sapiens R-HSA-2
- *Interferon alpha/beta signaling Homo sapiens R-HSA-909733
- *TCR signaling Homo sapiens R-HSA-202403
- *Costimulation by the CD28 family Homo sapiens R-HSA-388841
- *Translocation of ZAP-70 to Immunological synapse Homo sapiens R
- *PD-1 signaling Homo sapiens R-HSA-389948
- *Phosphorylation of CD3 and TCR zeta chains Homo sapiens R-HSA-
- *Antigen processing-Cross presentation Homo sapiens R-HSA-12369

(x-axis -log10P: 0, 20, 40, 60, 80)

Biological Processes

*Up-regulated in Wound_Healing_Immune_C1_*

- regulation of transcription, DNA-templated (GO:0006355)
- regulation of axonogenesis (GO:0050770)
- nervous system development (GO:0007399)
- epithelial cell development (GO:0002064)
- negative regulation of signal transduction (GO:0009968)
- mitral valve morphogenesis (GO:0003183)
- epithelial cell morphogenesis (GO:0003382)
- cell morphogenesis involved in differentiation (GO:0000904)
- regulation of retinoic acid receptor signaling pathway (GO:0048385)
- cytoskeleton organization (GO:0007010)
- synapse assembly (GO:0007416)
- kidney development (GO:0001822)
- negative regulation of cellular macromolecule biosynthetic process (GO:200
- extracellular matrix organization (GO:0030198)
- atrioventricular valve morphogenesis (GO:0003181)

(x-axis -log10P: 0, 1, 2, 3)

*Down-regulated in Wound_Healing_Immune_C1_*

- *cytokine-mediated signaling pathway (GO:0019221)
- *regulation of immune response (GO:0050776)
- *cellular response to interferon-gamma (GO:0071346)
- *interferon-gamma-mediated signaling pathway (GO:0060333)
- *inflammatory response (GO:0006954)
- *positive regulation of T cell activation (GO:0050870)
- *positive regulation of lymphocyte proliferation (GO:0050671)
- *regulation of T cell activation (GO:0050863)
- *antigen receptor-mediated signaling pathway (GO:0050851)
- *positive regulation of T cell proliferation (GO:0042102)
- *regulation of T cell proliferation (GO:0042129)
- *T cell receptor signaling pathway (GO:0050852)
- *cellular response to type I interferon (GO:0071357)
- *type I interferon signaling pathway (GO:0060337)
- *T cell activation (GO:0042110)

(x-axis -log10P: 0, 10, 20, 30, 40, 50)

KEGG Pathways

*Up-regulated in Wound_Healing_Immune_C1_*

- ECM-receptor interaction
- Wnt signaling pathway
- Mineral absorption
- Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Inositol phosphate metabolism
- Phosphatidylinositol signaling system
- Insulin secretion
- Endocrine and other factor-regulated calcium reabsorption
- Pancreatic secretion
- Axon guidance
- Hippo signaling pathway
- Pathogenic Escherichia coli infection
- ErbB signaling pathway
- Focal adhesion
- Human papillomavirus infection

(x-axis -log10P: 0, 0.5, 1, 1.5, 2, 2.5, 3)

*Down-regulated in Wound_Healing_Immune_C1_*

- *Antigen processing and presentation
- *Allograft rejection
- *Cell adhesion molecules (CAMs)
- *Graft-versus-host disease
- *Type I diabetes mellitus
- *Autoimmune thyroid disease
- *Viral myocarditis
- *Th1 and Th2 cell differentiation
- *Hematopoietic cell lineage
- *Th17 cell differentiation
- *Staphylococcus aureus infection
- *Natural killer cell mediated cytotoxicity
- *Intestinal immune network for IgA production
- *Primary immunodeficiency
- *Phagosome

(x-axis -log10P: 0, 5, 10, 15, 20, 25, 30)

S1B

Immunological Subtypes	Sample size
Wound Healing (C1)	22
Inflammatory (C3)	135

Down-regulated in Wound_Healing_Immune_C1_ Up-regulated in Wound_Healing_Immune_C1_

Gene symbol	logFC	AveExpr	t	P.Value
PAQR6	1.191942	0.344273	3.789672	2.14E-04
AFP	2.896023	3.312498	3.089215	2.37E-03
PAQR5	1.484179	2.100832	2.540652	1.20E-02
CCM3	0.200158	3.992807	2.209856	2.85E-02
PGRMC1	-1.14256	8.277952	-5.10998	9.15E-07
PGRMC2	-0.49476	6.458132	-3.84915	1.71E-04

Molecular Functions

Up-regulated in Wound_Healing_Immune_C1_

*DNA binding (GO:0003677)
*DNA-dependent ATPase activity (GO:0008094)
*tubulin binding (GO:0015631)
*DNA helicase activity (GO:0003678)
*microtubule binding (GO:0008017)
*single-stranded DNA-dependent ATPase activity (GO:0...
*microtubule motor activity (GO:0003777)
*protein-DNA loading ATPase activity (GO:0033170)
*DNA clamp loader activity (GO:0003689)
*ATP-dependent DNA helicase activity (GO:0004003)
*3'-5' DNA helicase activity (GO:0043138)
*RNA binding (GO:0003723)
*double-stranded DNA binding (GO:0003690)
*motor activity (GO:0003774)
*DNA secondary structure binding (GO:0000217)

Down-regulated in Wound_Healing_Immune_C1_

*oxidoreductase activity, acting on the CH-OH group of
*alcohol dehydrogenase (NAD) activity (GO:0004022)
*alcohol dehydrogenase activity, zinc-dependent (GO:0...
*oxidoreductase activity, acting on the aldehyde or oxo...
*oxidoreductase activity, acting on paired donors, with...
*NAD binding (GO:0051287)
*acyl-CoA dehydrogenase activity (GO:0003995)
*fatty acid ligase activity (GO:0015645)
*zinc ion binding (GO:0008270)
*oxidoreductase activity, acting on single donors with i...
*C-acyltransferase activity (GO:0016408)
*transition metal ion binding (GO:0046914)
*aldehyde dehydrogenase (NAD) activity (GO:0004029)
*fatty-acyl-CoA synthase activity (GO:0004321)
*acyl-CoA ligase activity (GO:0003996)

Reactome pathways

Up-regulated in Wound_Healing_Immune_C1_

*Cell Cycle Homo sapiens R-HSA-1640170
*Cell Cycle, Mitotic Homo sapiens R-HSA-69278
*M Phase Homo sapiens R-HSA-68886
*Mitotic Prometaphase Homo sapiens R-HSA-68877
*Resolution of Sister Chromatid Cohesion Homo sapiens
*Mitotic Metaphase and Anaphase Homo sapiens R-HSA-...
*RHO GTPases Activate Formins Homo sapiens R-HSA-5...
*Mitotic Anaphase Homo sapiens R-HSA-68882
*Separation of Sister Chromatids Homo sapiens R-HSA-...
*Cell Cycle Checkpoints Homo sapiens R-HSA-69620
*RHO GTPase Effectors Homo sapiens R-HSA-195258
*Signaling by Rho GTPases Homo sapiens R-HSA-19431...
*Activation of ATR in response to replication stress Hom...
*Mitotic G1-G1/S phases Homo sapiens R-HSA-453279
*G2/M Checkpoints Homo sapiens R-HSA-69481

Down-regulated in Wound_Healing_Immune_C1_

*Metabolism Homo sapiens R-HSA-1430728
*Metabolism of lipids and lipoproteins Homo sapiens R-...
*Biological oxidations Homo sapiens R-HSA-211859
*Phase 1 - Functionalization of compounds Homo sapien...
*Metabolism of amino acids and derivatives Homo sapie...
*Branched-chain amino acid catabolism Homo sapiens R...
*Intrinsic Pathway of Fibrin Clot Formation Homo sapie...
*Regulation of Complement cascade Homo sapiens R-HS...
*Ethanol oxidation Homo sapiens R-HSA-71384
*Formation of Fibrin Clot (Clotting Cascade) Homo sapie...
*Fatty acid, triacylglycerol, and ketone body metabolism...
*Histidine, lysine, phenylalanine, tyrosine, proline and t...
*Complement cascade Homo sapiens R-HSA-166658
*Metabolism of vitamins and cofactors Homo sapiens R-...
*Metabolism of water-soluble vitamins and cofactors Ho...

Biological Processes

Up-regulated in Wound_Healing_Immune_C1_

*DNA metabolic process (GO:0006259)
*DNA replication (GO:0006260)
*mitotic cell cycle phase transition (GO:0044772)
*mitotic sister chromatid segregation (GO:0000070)
*mitotic spindle organization (GO:0007052)
*cellular macromolecule biosynthetic process (GO:0034...
*microtubule cytoskeleton organization involved in mito...
*centromere complex assembly (GO:0034508)
*DNA repair (GO:0006281)
*G1/S transition of mitotic cell cycle (GO:0000082)
*chromatin remodeling at centromere (GO:0031055)
*cell cycle G1/S phase transition (GO:0044843)
*CENP-A containing nucleosome assembly (GO:003408C
*CENP-A containing chromatin organization (GO:006164...
*cellular response to DNA damage stimulus (GO:000697...

Down-regulated in Wound_Healing_Immune_C1_

*fatty acid metabolic process (GO:0006631)
*alpha-amino acid catabolic process (GO:1901606)
*fatty acid catabolic process (GO:0009062)
*branched-chain amino acid metabolic process (GO:000...
*monocarboxylic acid metabolic process (GO:0032787)
*cellular amino acid catabolic process (GO:0009063)
*dicarboxylic acid metabolic process (GO:0043648)
*fatty acid oxidation (GO:0019395)
*acyl-CoA metabolic process (GO:0006637)
*lipid transport (GO:0006869)
*coenzyme metabolic process (GO:0006732)
*branched-chain amino acid catabolic process (GO:0009...
*short-chain fatty acid catabolic process (GO:0019626)
*sulfur amino acid metabolic process (GO:0000096)
*short-chain fatty acid metabolic process (GO:0046459)

KEGG Pathways

Up-regulated in Wound_Healing_Immune_C1_

*Cell cycle
*DNA replication
*Oocyte meiosis
*Homologous recombination
*Progesterone-mediated oocyte maturation
*Spliceosome
*Fanconi anemia pathway
*Pyrimidine metabolism
*Mismatch repair
*Human T-cell leukemia virus 1 infection
*Cellular senescence
*p53 signaling pathway
*Small cell lung cancer
*Pathogenic Escherichia coli infection
*RNA transport

Down-regulated in Wound_Healing_Immune_C1_

*Complement and coagulation cascades
*Fatty acid degradation
*Valine, leucine and isoleucine degradation
*Tyrosine metabolism
*Peroxisome
*Propanoate metabolism
*Butanoate metabolism
*Glyoxylate and dicarboxylate metabolism
*beta-Alanine metabolism
*Tryptophan metabolism
*Glycolysis / Gluconeogenesis
*PPAR signaling pathway
*Pyruvate metabolism
*Glycine, serine and threonine metabolism
*Drug metabolism

S1C

Immunological Subtypes	Sample size
Wound Healing (C1)	22
Lymphocyte depleted (C4)	159

Gene symbol	logFC	AveExpr	t	P.Value
AFP	2.882463	3.183769	3.563241	4.67E-04
PAQR8	1.154065	1.557629	3.544084	5.00E-04
PAQR5	2.228739	1.326255	3.43325	7.37E-04
PAQR6	1.054751	0.347308	3.42513	7.58E-04
PGRMC1	-1.33634	8.378224	-6.01506	9.56E-09
PGRMC2	-0.64401	6.503715	-5.01827	1.23E-06
PAQR9	-0.8919	4.253548	-3.13713	1.99E-03
CCM2	-0.3834	6.047957	-2.40294	1.73E-02

Molecular Functions
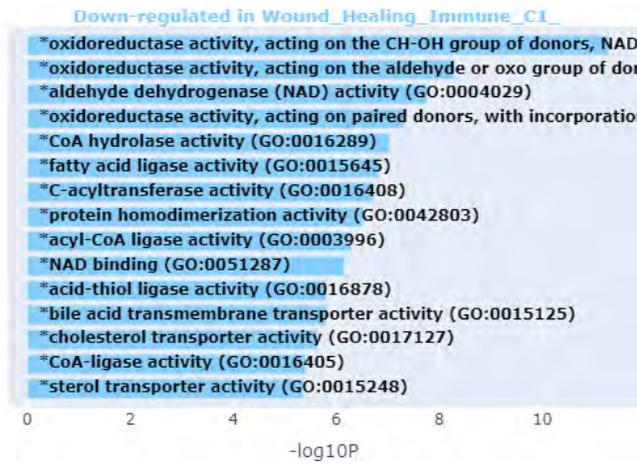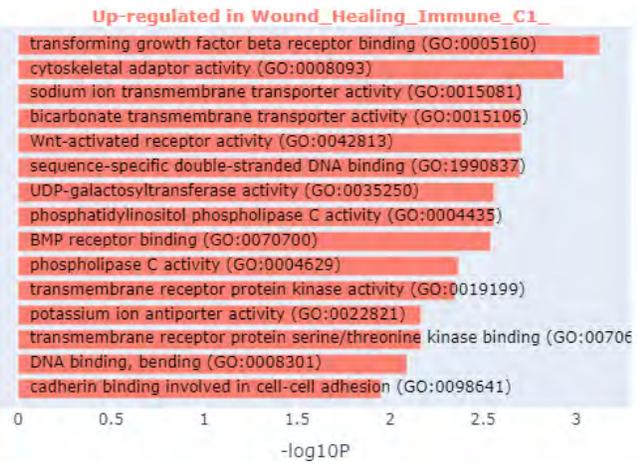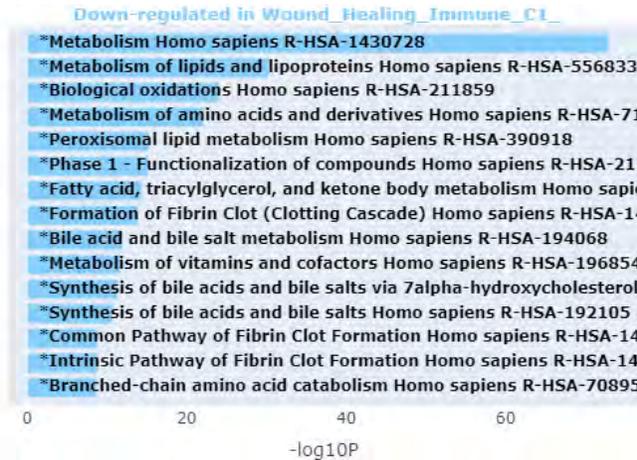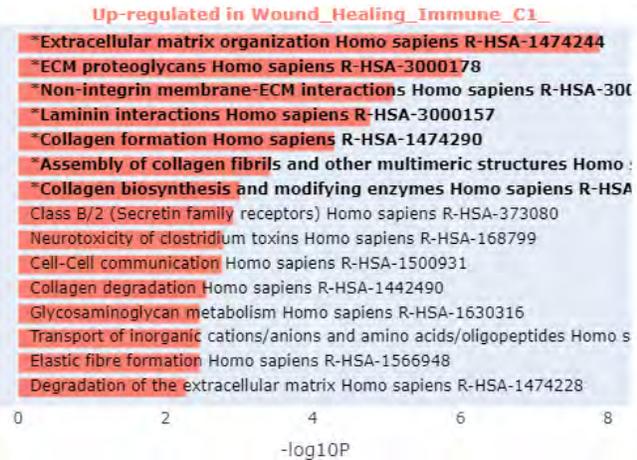
Reactome pathways
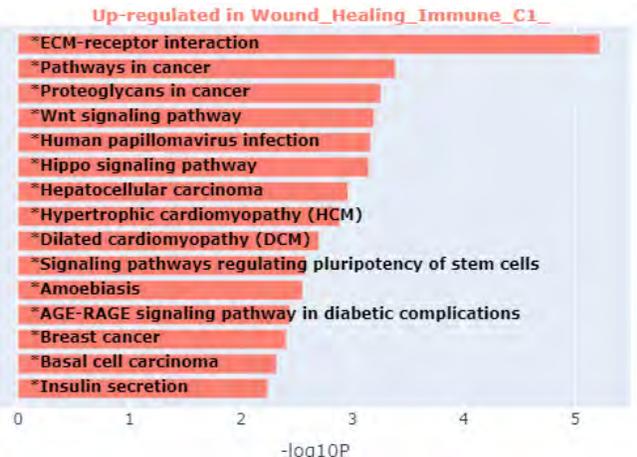
Biological Processes
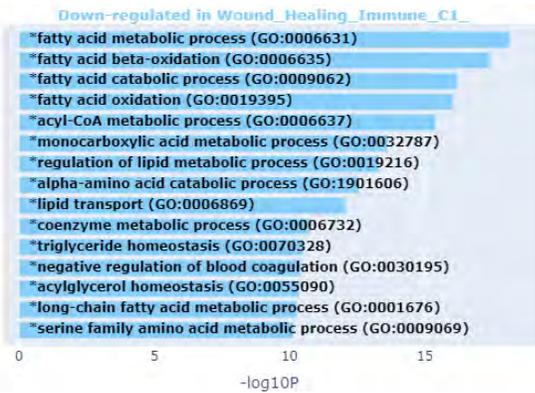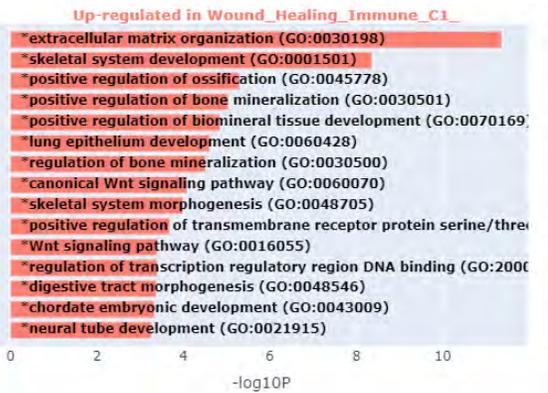
KEGG Pathways

S1D

Down-regulated in IFN_gamma_Dominant_Immune_C2_ Up-regulated in IFN_gamma_Dominant_Immune_C2_
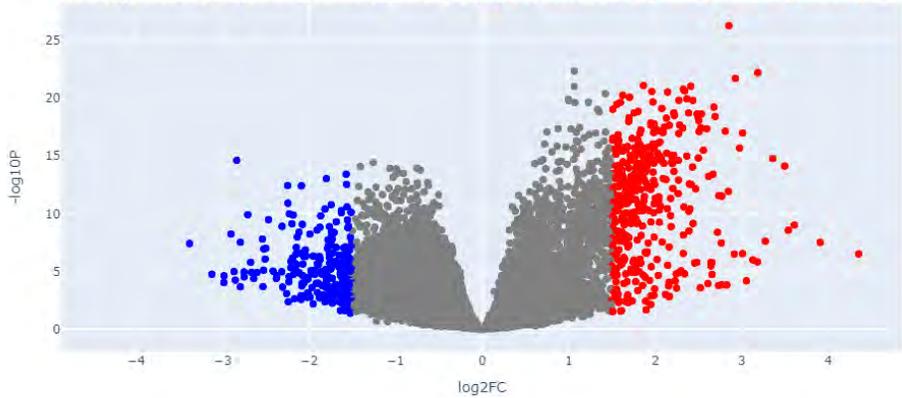
Gene symbol	logFC	AveExpr	t	P.Value
AFP	3.916882	3.872694	5.782277	3.16E-08
CCM3	0.153459	3.986799	2.163984	3.18E-02
PAQR6	0.500112	0.287465	2.111144	3.61E-02
PAQR8	0.42792	2.253244	2.005111	4.64E-02
PGRMC1	-0.7814	8.228141	-4.66774	5.90E-06
CCM1	-0.47107	3.94761	-4.57818	8.68E-06
nPRs	-0.98985	-1.40387	-2.97771	3.30E-03
PGRMC2	-0.29999	6.436494	-2.93692	3.74E-03

Molecular Functions

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *kinase binding (GO:0019900)
- *MHC protein binding (GO:0042287)
- *MHC class II receptor activity (GO:0032395)
- *MHC class II protein complex binding (GO:0023026)
- *chemokine activity (GO:0008009)
- *double-stranded DNA binding (GO:0003690)
- *MHC protein complex binding (GO:0023023)
- *chemokine receptor binding (GO:0042379)
- *MHC class I protein binding (GO:0042288)
- *DNA secondary structure binding (GO:0000217)
- *microtubule binding (GO:0008017)
- *3'-5' DNA helicase activity (GO:0043138)
- *single-stranded DNA binding (GO:0003697)
- *tubulin binding (GO:0015631)
- *DNA binding (GO:0003677)

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *Rho guanyl-nucleotide exchange factor activity (GO:0005089)
- *transcription regulatory region sequence-specific DNA binding (GO
- *core promoter sequence-specific DNA binding (GO:0001046)
- *ligand-dependent nuclear receptor binding (GO:0016922)
- *core promoter binding (GO:0001047)
- *RNA polymerase II transcription factor binding (GO:0001085)
- *RNA polymerase binding (GO:0070063)
- cadherin binding (GO:0045296)
- ribosome binding (GO:0043022)
- protein kinase activity (GO:0004672)
- microtubule plus-end binding (GO:0051010)
- cAMP binding (GO:0030552)
- GTPase regulator activity (GO:0030695)
- transmembrane receptor protein tyrosine kinase activity (GO:0004714)
- PDZ domain binding (GO:0030165)

Reactome pathways

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *Cell Cycle Homo sapiens R-HSA-1640170
- *Cell Cycle, Mitotic Homo sapiens R-HSA-69278
- *Immune System Homo sapiens R-HSA-168256
- *Mitotic Prometaphase Homo sapiens R-HSA-68877
- *Adaptive Immune System Homo sapiens R-HSA-1280218
- *Resolution of Sister Chromatid Cohesion Homo sapiens R-HSA-2500
- *M Phase Homo sapiens R-HSA-68886
- *Signaling by Rho GTPases Homo sapiens R-HSA-194315
- *Mitotic G1-G1/S phases Homo sapiens R-HSA-453279
- *RHO GTPase Effectors Homo sapiens R-HSA-195258
- *G1/S Transition Homo sapiens R-HSA-69206
- *Mitotic Metaphase and Anaphase Homo sapiens R-HSA-2555396
- *Mitotic Anaphase Homo sapiens R-HSA-68882
- *DNA Replication Homo sapiens R-HSA-69306
- *DNA strand elongation Homo sapiens R-HSA-69190

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *RORA activates gene expression Homo sapiens R-HSA-1368082
- *BMAL1:CLOCK,NPAS2 activates circadian gene expression Homo sa
- *Circadian Clock Homo sapiens R-HSA-400253
- *Rho GTPase cycle Homo sapiens R-HSA-194840
- *YAP1- and WWTR1 (TAZ)-stimulated gene expression Homo sapien
- *Pre-NOTCH Expression and Processing Homo sapiens R-HSA-19124
- *PPARA activates gene expression Homo sapiens R-HSA-1989781
- *Signaling by Rho GTPases Homo sapiens R-HSA-194315
- *Regulation of lipid metabolism by Peroxisome proliferator-activated
- *Signaling by NOTCH Homo sapiens R-HSA-157118
- *Pre-NOTCH Processing in the Endoplasmic Reticulum Homo sapiens
- *Pre-NOTCH Transcription and Translation Homo sapiens R-HSA-191
- *RNF mutants show enhanced WNT signaling and proliferation Homo
- *Signal Transduction Homo sapiens R-HSA-162582
- *NRAGE signals death through JNK Homo sapiens R-HSA-193648

Biological Processes

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *DNA metabolic process (GO:0006259)
- *mitotic cell cycle phase transition (GO:0044772)
- *DNA replication (GO:0006260)
- *G1/S transition of mitotic cell cycle (GO:0000082)
- *cytokine-mediated signaling pathway (GO:0019221)
- *positive regulation of lymphocyte proliferation (GO:0050671)
- *cellular response to interferon-gamma (GO:0071346)
- *antigen processing and presentation of exogenous peptide antigen
- *antigen processing and presentation of exogenous peptide antigen
- *antigen processing and presentation of peptide antigen via MHC cla
- *positive regulation of T cell activation (GO:0050870)
- *positive regulation of T cell proliferation (GO:0042102)
- *cell cycle G1/S phase transition (GO:0044843)
- *mitotic sister chromatid segregation (GO:0000070)
- *mitotic spindle organization (GO:0007052)

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *cytoskeleton organization (GO:0007010)
- *regulation of fatty acid oxidation (GO:0046320)
- *regulation of small GTPase mediated signal transduction (GO:0051
- *positive regulation of cell migration (GO:0030335)
- *cellular response to growth factor stimulus (GO:0071363)
- *positive regulation of epithelial cell migration (GO:0010634)
- *regulation of anatomical structure morphogenesis (GO:0022603)
- *cardiocyte differentiation (GO:0035051)
- *negative regulation of cytoplasmic translation (GO:2000766)
- *fatty acid metabolic process (GO:0006631)
- *regulation of Notch signaling pathway (GO:0008593)
- *Notch signaling pathway (GO:0007219)
- *regulation of intracellular signal transduction (GO:1902531)
- *positive regulation of substrate adhesion-dependent cell spreading
- *positive regulation of protein localization to plasma membrane (GO

KEGG Pathways

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *Cell cycle
- *Th1 and Th2 cell differentiation
- *Type I diabetes mellitus
- *Primary immunodeficiency
- *Th17 cell differentiation
- *Allograft rejection
- *Graft-versus-host disease
- *Human T-cell leukemia virus 1 infection
- *Leishmaniasis
- *Antigen processing and presentation
- *Autoimmune thyroid disease
- *Cell adhesion molecules (CAMs)
- *Inflammatory bowel disease (IBD)
- *Hematopoietic cell lineage
- *Intestinal immune network for IgA production

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *Adherens junction
- *Breast cancer
- *Endometrial cancer
- *Rap1 signaling pathway
- *Insulin resistance
- *mTOR signaling pathway
- *FoxO signaling pathway
- *Regulation of actin cytoskeleton
- *Prostate cancer
- Focal adhesion
- Non-small cell lung cancer
- Notch signaling pathway
- Renal cell carcinoma
- Insulin signaling pathway
- Thyroid hormone signaling pathway

S1E

Immunological Subtypes	Sample size
IFN-γ dominant (C2)	45
Lymphocyte depleted (C4)	159

Down-regulated in IFN_gamma_Dominant_Immune_C2_   Up-regulated in IFN_gamma_Dominant_Immune_C2_

Gene symbol	logFC	AveExpr	t	P.Value
AFP	3.921464	3.692572	6.630822	2.88E-10
PAQR8	1.116469	1.652463	4.713229	4.48E-06
PAQR5	1.129452	1.295504	2.361378	1.91E-02
CCM1	-0.37457	3.833406	-3.77653	2.08E-04
PGRMC1	-0.9364	8.322968	-5.7336	3.47E-08
PGRMC2	-0.40891	6.479483	-4.12465	5.39E-05

Molecular Functions

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *MHC class II receptor activity (GO:0032395)
- *MHC protein binding (GO:0042287)
- *cytokine receptor activity (GO:0004896)
- *MHC protein complex binding (GO:0023023)
- *CCR chemokine receptor binding (GO:0048020)
- *MHC class II protein complex binding (GO:0023026)
- *non-membrane spanning protein tyrosine kinase activity (GO:0004
- *chemokine activity (GO:0008009)
- *chemokine receptor binding (GO:0042379)
- *MHC class I protein binding (GO:0042288)
- *phosphatidylinositol-3,4-bisphosphate binding (GO:0043325)
- *T cell receptor binding (GO:0042608)
- *phosphatidylinositol-4,5-bisphosphate 3-kinase activity (GO:00469
- *chemokine receptor activity (GO:0004950)
- *phosphatidylinositol bisphosphate kinase activity (GO:0052813)

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *acyl-CoA dehydrogenase activity (GO:0003995)
- *oxidoreductase activity, acting on the CH-OH group of donors, NAD
- *flavin adenine dinucleotide binding (GO:0050660)
- *NAD binding (GO:0051287)
- *oxidoreductase activity, acting on the aldehyde or oxo group of don
- *oxidoreductase activity, acting on paired donors, with incorporatio
- *aldehyde dehydrogenase (NAD) activity (GO:0004029)
- *heme binding (GO:0020037)
- *acyl-CoA oxidase activity (GO:0003997)
- *retinoic acid binding (GO:0001972)
- *fatty-acyl-CoA synthase activity (GO:0004321)
- *hydrolase activity, acting on acid anhydrides, catalyzing transmeml
- *anion:cation symporter activity (GO:0015296)
- *acyl-CoA ligase activity (GO:0003996)
- *3-chloroallyl aldehyde dehydrogenase activity (GO:0004028)

Reactome pathways

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *Immune System Homo sapiens R-HSA-168256
- *Adaptive Immune System Homo sapiens R-HSA-1280218
- *Immunoregulatory interactions between a Lymphoid and a non-Lyn
- *Generation of second messenger molecules Homo sapiens R-HSA-2
- *PD-1 signaling Homo sapiens R-HSA-389948
- *Costimulation by the CD28 family Homo sapiens R-HSA-388841
- *Translocation of ZAP-70 to Immunological synapse Homo sapiens R
- *Phosphorylation of CD3 and TCR zeta chains Homo sapiens R-HSA-2
- *TCR signaling Homo sapiens R-HSA-202403
- *Hemostasis Homo sapiens R-HSA-109582
- *Innate Immune System Homo sapiens R-HSA-168249
- *Cytokine Signaling in Immune system Homo sapiens R-HSA-128021
- *GPVI-mediated activation cascade Homo sapiens R-HSA-114604
- *Downstream TCR signaling Homo sapiens R-HSA-202424
- *Cell surface interactions at the vascular wall Homo sapiens R-HSA-2

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *Metabolism Homo sapiens R-HSA-1430728
- *Biological oxidations Homo sapiens R-HSA-211859
- *Metabolism of amino acids and derivatives Homo sapiens R-HSA-71
- *Metabolism of lipids and lipoproteins Homo sapiens R-HSA-556833
- *Phase II conjugation Homo sapiens R-HSA-156580
- *Phase 1 - Functionalization of compounds Homo sapiens R-HSA-21
- *Branched-chain amino acid catabolism Homo sapiens R-HSA-70895
- *Sulfur amino acid metabolism Homo sapiens R-HSA-1614635
- *Fatty acid, triacylglycerol, and ketone body metabolism Homo sapie
- *Histidine, lysine, phenylalanine, tyrosine, proline and tryptophan ca
- *Phenylalanine and tyrosine catabolism Homo sapiens R-HSA-71182
- *Bile acid and bile salt metabolism Homo sapiens R-HSA-194068
- *Metabolism of water-soluble vitamins and cofactors Homo sapiens
- *Peroxisomal lipid metabolism Homo sapiens R-HSA-390918
- *Conjugation of salicylate with glycine Homo sapiens R-HSA-177128

Biological Processes

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *inflammatory response (GO:0006954)
- *regulation of immune response (GO:0050776)
- *cytokine-mediated signaling pathway (GO:0019221)
- *positive regulation of T cell activation (GO:0050870)
- *positive regulation of T cell proliferation (GO:0042102)
- *positive regulation of lymphocyte proliferation (GO:0050671)
- *antigen receptor-mediated signaling pathway (GO:0050851)
- *cellular response to interferon-gamma (GO:0071346)
- *regulation of T cell proliferation (GO:0042129)
- *neutrophil activation involved in immune response (GO:0002283)
- *neutrophil degranulation (GO:0043312)
- *T cell activation (GO:0042110)
- *neutrophil mediated immunity (GO:0002446)
- *cellular response to cytokine stimulus (GO:0071345)
- *T cell receptor signaling pathway (GO:0050852)

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *fatty acid beta-oxidation (GO:0006635)
- *fatty acid catabolic process (GO:0009062)
- *fatty acid oxidation (GO:0019395)
- *cellular amino acid catabolic process (GO:0009063)
- *fatty acid metabolic process (GO:0006631)
- *fatty acid beta-oxidation using acyl-CoA dehydrogenase (GO:00335
- *branched-chain amino acid catabolic process (GO:0009083)
- *regulation of lipid metabolic process (GO:0019216)
- *fatty acid beta-oxidation using acyl-CoA oxidase (GO:0033540)
- *sulfur amino acid metabolic process (GO:0000096)
- *branched-chain amino acid metabolic process (GO:0009081)
- *serine family amino acid metabolic process (GO:0009069)
- *L-phenylalanine metabolic process (GO:0006558)
- *L-phenylalanine catabolic process (GO:0006559)
- *erythrose 4-phosphate/phosphoenolpyruvate family amino acid cat

KEGG Pathways

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *Hematopoietic cell lineage
- *Th1 and Th2 cell differentiation
- *Th17 cell differentiation
- *Cell adhesion molecules (CAMs)
- *Chemokine signaling pathway
- *Leishmaniasis
- *Cytokine-cytokine receptor interaction
- *Allograft rejection
- *Graft-versus-host disease
- *Type I diabetes mellitus
- *Primary immunodeficiency
- *Staphylococcus aureus infection
- *Natural killer cell mediated cytotoxicity
- *T cell receptor signaling pathway
- *Intestinal immune network for IgA production

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *Peroxisome
- *Valine, leucine and isoleucine degradation
- *beta-Alanine metabolism
- *Drug metabolism
- *Propanoate metabolism
- *Fatty acid degradation
- *PPAR signaling pathway
- *Primary bile acid biosynthesis
- *Ascorbate and aldarate metabolism
- *Butanoate metabolism
- *Pyruvate metabolism
- *Retinol metabolism
- *Tryptophan metabolism
- *Metabolism of xenobiotics by cytochrome P450
- *Cysteine and methionine metabolism

S1F

Immunological Subtypes	Sample size
Inflammatory (C3)	135
Lymphocyte depleted (C4)	159

Down-regulated in Inflammatory_Immune_C3_   Up-regulated in Inflammatory_Immune_C3_

(volcano plot with axes -log10P vs log2FC)

Gene symbol	logFC	AveExpr	t	P.Value
nPRs	1.510682	-2.04635	6.092938	3.45E-09
PAQR8	0.684746	1.709085	4.151653	4.32E-05
PAQR5	0.776807	1.385898	2.33205	2.04E-02
CCM2	-0.20795	5.975757	-2.57951	1.04E-02
CCM3	-0.1836	3.980731	-3.29313	1.11E-03

Molecular Functions

Up-regulated in Inflammatory_Immune_C3_
*platelet-derived growth factor binding (GO:0048407)
*transmembrane receptor protein tyrosine kinase activity (GO:0004
*protein tyrosine kinase activity (GO:0004713)
*transmembrane receptor protein kinase activity (GO:0019199)
*collagen binding (GO:0005518)
*mitogen-activated protein kinase kinase binding (GO:0031434)
*integrin binding (GO:0005178)
*MAP kinase kinase kinase activity (GO:0004709)
*protein kinase binding (GO:0019901)
*protein kinase activity (GO:0004672)
*phospholipase C activity (GO:0004629)
*transcription factor activity, RNA polymerase II core promoter prox
*RNA polymerase II transcription factor binding (GO:0001085)
*phosphatidylinositol phospholipase C activity (GO:0004435)
*phosphatidylinositol-4,5-bisphosphate 3-kinase activity (GO:00469
(x-axis: -log10P)

Down-regulated in Inflammatory_Immune_C3_
*RNA binding (GO:0003723)
*TBP-class protein binding (GO:0017025)
*proteasome-activating ATPase activity (GO:0036402)
*translation initiation factor activity (GO:0003743)
*methyltransferase activity (GO:0008168)
*translation factor activity, RNA binding (GO:0008135)
*exoribonuclease activity, producing 5'-phosphomonoesters (GO:00
*DNA helicase activity (GO:0003678)
*ATP-dependent DNA helicase activity (GO:0004003)
*rRNA binding (GO:0019843)
*rRNA methyltransferase activity (GO:0008649)
*snoRNA binding (GO:0030515)
*3'-5'-exoribonuclease activity (GO:0000175)
*ATP-dependent helicase activity (GO:0008026)
*adenylyltransferase activity (GO:0070566)
(x-axis: -log10P)

Reactome pathways

Up-regulated in Inflammatory_Immune_C3_
*Extracellular matrix organization Homo sapiens R-HSA-1474244
*Hemostasis Homo sapiens R-HSA-109582
*Collagen biosynthesis and modifying enzymes Homo sapiens R-HSA-
*Collagen formation Homo sapiens R-HSA-1474290
*Diseases of glycosylation Homo sapiens R-HSA-3781865
*Assembly of collagen fibrils and other multimeric structures Homo
*Signal Transduction Homo sapiens R-HSA-162582
*Platelet activation, signaling and aggregation Homo sapiens R-HSA-
*ECM proteoglycans Homo sapiens R-HSA-3000178
*Diseases associated with glycosaminoglycan metabolism Homo sap
*Platelet homeostasis Homo sapiens R-HSA-418346
*Elastic fibre formation Homo sapiens R-HSA-1566948
*Integrin cell surface interactions Homo sapiens R-HSA-216083
*Developmental Biology Homo sapiens R-HSA-1266738
*G alpha (z) signalling events Homo sapiens R-HSA-418597
(x-axis: -log10P)

Down-regulated in Inflammatory_Immune_C3_
*Cell Cycle Homo sapiens R-HSA-1640170
*Synthesis of DNA Homo sapiens R-HSA-69239
*DNA Replication Homo sapiens R-HSA-69306
*S Phase Homo sapiens R-HSA-69242
*Cell Cycle, Mitotic Homo sapiens R-HSA-69278
*Gene Expression Homo sapiens R-HSA-74160
*DNA Replication Pre-Initiation Homo sapiens R-HSA-69002
*M/G1 Transition Homo sapiens R-HSA-68874
*G1/S Transition Homo sapiens R-HSA-69206
*Mitotic G1-G1/S phases Homo sapiens R-HSA-453279
*Mitotic Anaphase Homo sapiens R-HSA-68882
*Mitotic Metaphase and Anaphase Homo sapiens R-HSA-2555396
*Separation of Sister Chromatids Homo sapiens R-HSA-2467813
*APC/C:Cdc20 mediated degradation of Securin Homo sapiens R-HS
*Assembly of the pre-replicative complex Homo sapiens R-HSA-6886
(x-axis: -log10P)

Biological Processes

Up-regulated in Inflammatory_Immune_C3_
*extracellular matrix organization (GO:0030198)
*negative regulation of signal transduction (GO:0009968)
*circulatory system development (GO:0072359)
*positive regulation of kinase activity (GO:0033674)
*peptidyl-tyrosine phosphorylation (GO:0018108)
*positive regulation of MAPK cascade (GO:0043410)
*positive regulation of ERK1 and ERK2 cascade (GO:0070374)
*peptidyl-tyrosine modification (GO:0018212)
*T cell activation (GO:0042110)
*regulation of ERK1 and ERK2 cascade (GO:0070372)
*cellular response to cytokine stimulus (GO:0071345)
*regulation of angiogenesis (GO:0045765)
*positive regulation of cell motility (GO:2000147)
*regulation of cell migration (GO:0030334)
*positive regulation of intracellular signal transduction (GO:190253
(x-axis: -log10P)

Down-regulated in Inflammatory_Immune_C3_
*negative regulation of ubiquitin protein ligase activity (GO:190466
*anaphase-promoting complex-dependent catabolic process (GO:00
*negative regulation of ubiquitin-protein ligase activity involved in r
*regulation of ubiquitin-protein ligase activity involved in mitotic cel
*positive regulation of ubiquitin-protein ligase activity involved in re
*regulation of cellular amine metabolic process (GO:0033238)
*regulation of cellular amino acid metabolic process (GO:0006521)
*negative regulation of cell cycle G2/M phase transition (GO:190275
*negative regulation of G2/M transition of mitotic cell cycle (GO:001
*positive regulation of ubiquitin protein ligase activity (GO:1904668
*positive regulation of protein ubiquitination involved in ubiquitin-d
*regulation of cellular ketone metabolic process (GO:0010565)
*regulation of mitotic cell cycle phase transition (GO:1901990)
*regulation of G2/M transition of mitotic cell cycle (GO:0010389)
*regulation of mRNA stability (GO:0043488)
(x-axis: -log10P)

KEGG Pathways

Up-regulated in Inflammatory_Immune_C3_
*PI3K-Akt signaling pathway
*Focal adhesion
*Pathways in cancer
*Platelet activation
*Chemokine signaling pathway
*cGMP-PKG signaling pathway
*ECM-receptor interaction
*Protein digestion and absorption
*Apelin signaling pathway
*Relaxin signaling pathway
*Vascular smooth muscle contraction
*AGE-RAGE signaling pathway in diabetic complications
*Rap1 signaling pathway
*Human papillomavirus infection
*Primary immunodeficiency
(x-axis: -log10P)

Down-regulated in Inflammatory_Immune_C3_
*Proteasome
*DNA replication
*RNA transport
*Mismatch repair
*Spliceosome
*Cell cycle
*Fanconi anemia pathway
*Homologous recombination
*RNA degradation
*Nucleotide excision repair
*Ribosome biogenesis in eukaryotes
*Ribosome
Thermogenesis
Oxidative phosphorylation
mRNA surveillance pathway
(x-axis: -log10P)

S2A

Immunological Subtypes	Sample size
Wound Healing (C1)	7
IFN-γ dominant (C2)	2

Down-regulated in Wound_Healing_Immune_C1_   Up-regulated in Wound_Healing_Immune_C1_

-log10P

log2FC

Molecular Functions

Up-regulated in Wound_Healing_Immune_C1_
- *protease binding (GO:0002020)
- *platelet-derived growth factor binding (GO:0048407)
- *protein kinase inhibitor activity (GO:0004860)
- *arylesterase activity (GO:0004064)
- *calcium ion binding (GO:0005509)
- *FK506 binding (GO:0005528)
- *cadherin binding (GO:0045296)
- *metalloendopeptidase activity (GO:0004222)
- *dolichyl-diphosphooligosaccharide-protein glycotransferase activity
- *acetylgalactosaminyltransferase activity (GO:0008376)
- *oligosaccharyl transferase activity (GO:0004576)
- *oxidoreductase activity, oxidizing metal ions, NAD or NADP as acce
- *protein binding involved in cell-cell adhesion (GO:0098632)
- *collagen binding (GO:0005518)
- *metal ion binding (GO:0046872)

-log10P

Down-regulated in Wound_Healing_Immune_C1_
- *MHC protein complex binding (GO:0023023)
- *T cell receptor binding (GO:0042608)
- *non-membrane spanning protein tyrosine kinase activity (GO:0004
- *phosphatidylinositol-3,4-bisphosphate binding (GO:0043325)
- *MHC class II protein complex binding (GO:0023026)
- *cytokine receptor activity (GO:0004896)
- *death receptor activity (GO:0005035)
- *tumor necrosis factor-activated receptor activity (GO:0005031)
- *SH3/SH2 adaptor activity (GO:0005070)
- *superoxide-generating NADPH oxidase activator activity (GO:0016
- *SH3 domain binding (GO:0017124)
- *GTPase regulator activity (GO:0030695)
- *MHC protein binding (GO:0042287)
- *chemokine activity (GO:0008009)
- *phosphatidylinositol phosphate binding (GO:1901981)

-log10P

Reactome pathways

Up-regulated in Wound_Healing_Immune_C1_
- *Extracellular matrix organization Homo sapiens R-HSA-1474244
- *Collagen formation Homo sapiens R-HSA-1474290
- *Collagen biosynthesis and modifying enzymes Homo sapiens R-HSA-
- *Assembly of collagen fibrils and other multimeric structures Homo s
- *Unfolded Protein Response (UPR) Homo sapiens R-HSA-381119
- *Post-translational protein modification Homo sapiens R-HSA-59759
- *Metabolism of proteins Homo sapiens R-HSA-392499
- *Cell junction organization Homo sapiens R-HSA-446728
- *IRE1alpha activates chaperones Homo sapiens R-HSA-381070
- *Platelet degranulation Homo sapiens R-HSA-114608
- *Response to elevated platelet cytosolic Ca2+ Homo sapiens R-HSA-
- *ATF6-alpha activates chaperones Homo sapiens R-HSA-381033
- *O-linked glycosylation of mucins Homo sapiens R-HSA-913709
- *Vesicle-mediated transport Homo sapiens R-HSA-5653656
- *XBP1(S) activates chaperone genes Homo sapiens R-HSA-381038

-log10P

Down-regulated in Wound_Healing_Immune_C1_
- *Immune System Homo sapiens R-HSA-168256
- *Adaptive Immune System Homo sapiens R-HSA-1280218
- *Immunoregulatory interactions between a Lymphoid and a non-Lyr
- *Cytokine Signaling in Immune system Homo sapiens R-HSA-128027
- *Generation of second messenger molecules Homo sapiens R-HSA-2
- *Costimulation by the CD28 family Homo sapiens R-HSA-388841
- *TCR signaling Homo sapiens R-HSA-202403
- *Phosphorylation of CD3 and TCR zeta chains Homo sapiens R-HSA-
- *PD-1 signaling Homo sapiens R-HSA-389948
- *TNFR2 non-canonical NF-kB pathway Homo sapiens R-HSA-566854
- *Antigen activates B Cell Receptor (BCR) leading to generation of se
- *Translocation of ZAP-70 to Immunological synapse Homo sapiens F
- *Innate Immune System Homo sapiens R-HSA-168249
- *TNFs bind their physiological receptors Homo sapiens R-HSA-56690
- *Chemokine receptors bind chemokines Homo sapiens R-HSA-38010

-log10P

Biological Processes

Up-regulated in Wound_Healing_Immune_C1_
- *extracellular matrix organization (GO:0030198)
- *collagen fibril organization (GO:0030199)
- *positive regulation of cell migration (GO:0030335)
- *endodermal cell differentiation (GO:0035987)
- *positive regulation of cell motility (GO:2000147)
- *protein complex subunit organization (GO:0071822)
- *regulation of cell migration (GO:0030334)
- *regulation of branching involved in ureteric bud morphogenesis (G(
- *endoderm formation (GO:0001706)
- *epidermis development (GO:0008544)
- *ATF6-mediated unfolded protein response (GO:0036500)
- *positive regulation of transcription from RNA polymerase II promot
- *skeletal system development (GO:0001501)
- *IRE1-mediated unfolded protein response (GO:0036498)
- *response to unfolded protein (GO:0006986)

-log10P

Down-regulated in Wound_Healing_Immune_C1_
- *regulation of immune response (GO:0050776)
- *B cell activation (GO:0042113)
- *cytokine-mediated signaling pathway (GO:0019221)
- *antigen receptor-mediated signaling pathway (GO:0050851)
- *T cell activation (GO:0042110)
- *positive regulation of T cell activation (GO:0050870)
- *T cell receptor signaling pathway (GO:0050852)
- *positive regulation of lymphocyte proliferation (GO:0050671)
- *lymphocyte differentiation (GO:0030098)
- *inflammatory response (GO:0006954)
- *positive regulation of T cell proliferation (GO:0042102)
- *regulation of T cell proliferation (GO:0042129)
- *cellular response to tumor necrosis factor (GO:0071356)
- *cellular response to cytokine stimulus (GO:0071345)
- *regulation of T cell activation (GO:0050863)

-log10P

KEGG Pathways

Up-regulated in Wound_Healing_Immune_C1_
- *Protein processing in endoplasmic reticulum
- *ECM-receptor interaction
- *Focal adhesion
- *Amoebiasis
- *Protein digestion and absorption
- *AGE-RAGE signaling pathway in diabetic complications
- *PI3K-Akt signaling pathway
- *Thyroid hormone synthesis
- *Complement and coagulation cascades
- Phenylalanine, tyrosine and tryptophan biosynthesis
- Arginine and proline metabolism
- Estrogen signaling pathway
- Nitrogen metabolism
- Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Human papillomavirus infection

-log10P

Down-regulated in Wound_Healing_Immune_C1_
- *Hematopoietic cell lineage
- *Primary immunodeficiency
- *Intestinal immune network for IgA production
- *Epstein-Barr virus infection
- *Cell adhesion molecules (CAMs)
- *NF-kappa B signaling pathway
- *Th1 and Th2 cell differentiation
- *Cytokine-cytokine receptor interaction
- *B cell receptor signaling pathway
- *Th17 cell differentiation
- *Chemokine signaling pathway
- *T cell receptor signaling pathway
- *Natural killer cell mediated cytotoxicity
- *Viral myocarditis
- *Human T-cell leukemia virus 1 infection

-log10P

S2B

Immunological Subtypes	Sample size
Wound Healing (C1)	7
Inflammatory (C3)	17

Gene symbol	logFC	AveExpr	t	P.Value
PAQR6	-1.3678	2.986596	-2.77353	1.02E-02
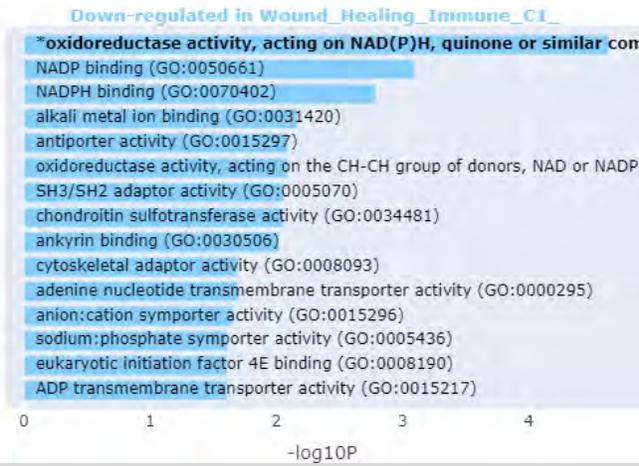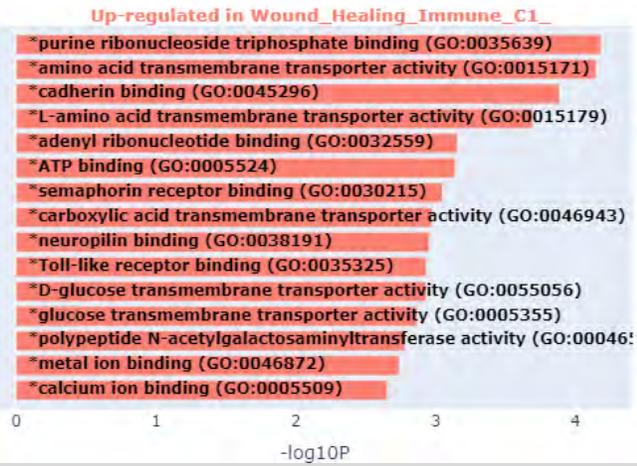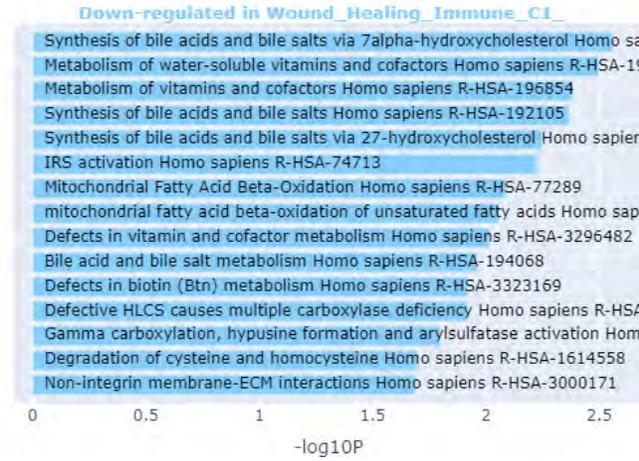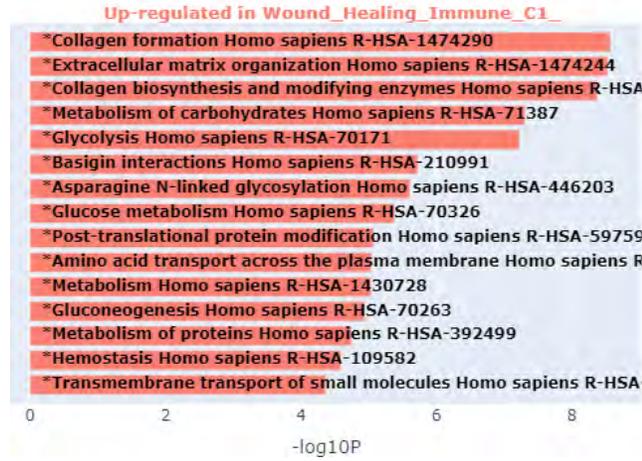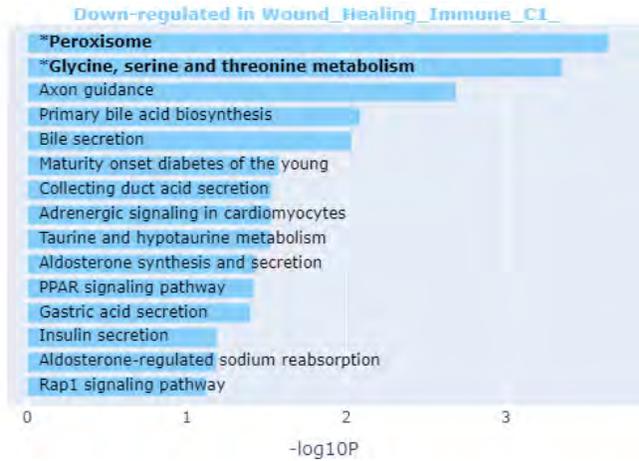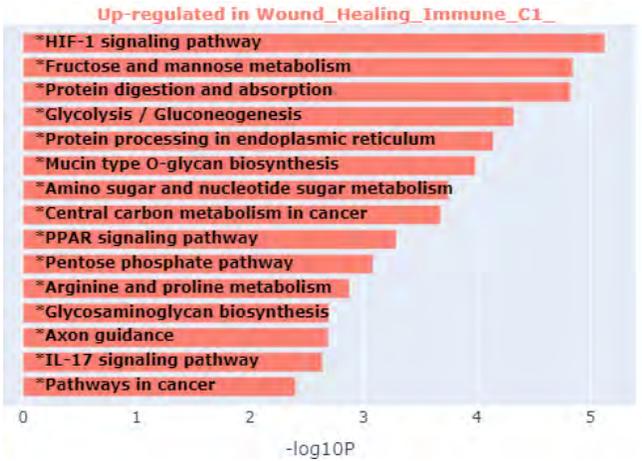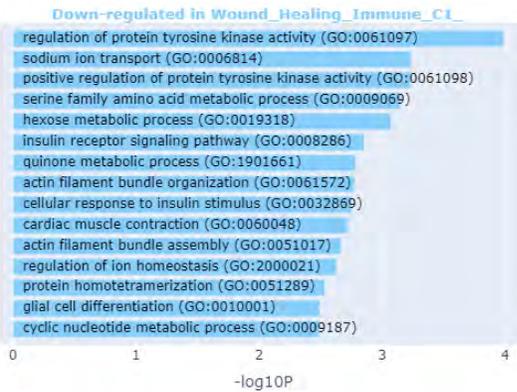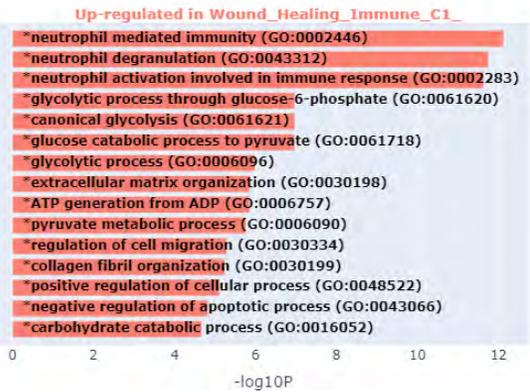
S2C

Immunological Subtypes	Sample size
Wound Healing (C1)	7
Lymphocyte depleted (C4)	8

Down-regulated in Wound_Healing_Immune_C1_   Up-regulated in Wound_Healing_Immune_C1_

-log10P

log2FC
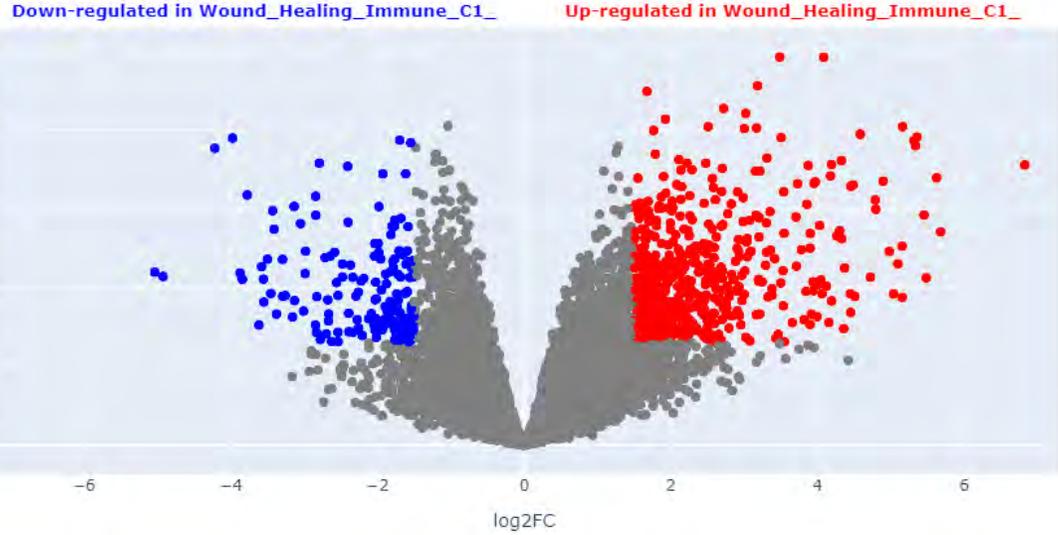
Gene symbol	logFC	AveExpr	t	P.Value
PAQR6	-1.47789	2.709641	-2.59804	1.90E-02

Molecular Functions

Up-regulated in Wound_Healing_Immune_C1_
*integrin binding (GO:0005178)
*protease binding (GO:0002020)
*GTP-Rho binding (GO:0017049)
*Rho GTPase binding (GO:0017048)
*platelet-derived growth factor binding (GO:0048407)
*calcium ion binding (GO:0005509)
*metal ion binding (GO:0046872)
*cytokine activity (GO:0005125)
*semaphorin receptor binding (GO:0030215)
*metallopeptidase activity (GO:0008237)
*neuropilin binding (GO:0038191)
*metalloendopeptidase activity (GO:0004222)
*Toll-like receptor binding (GO:0035325)
*vascular endothelial growth factor receptor binding (GO:0005172)
*calcium channel inhibitor activity (GO:0019855)

-log10P

Down-regulated in Wound_Healing_Immune_C1_
*NADH dehydrogenase (ubiquinone) activity (GO:0008137)
*NADH dehydrogenase (quinone) activity (GO:0050136)
*proton-transporting ATP synthase activity, rotational mechanism (
*cation-transporting ATPase activity (GO:0019829)
*hydro-lyase activity (GO:0016836)
*acetyl-CoA C-acyltransferase activity (GO:0003988)
*ATPase activity, coupled to transmembrane movement of ions, rota
*enoyl-CoA hydratase activity (GO:0004300)
*hydrogen ion transmembrane transporter activity (GO:0015078)
*NADH dehydrogenase activity (GO:0003954)
antiporter activity (GO:0015297)
oxidoreductase activity, acting on the CH-CH group of donors, NAD or NADP
voltage-gated anion channel activity (GO:0008308)
3-hydroxyacyl-CoA dehydrogenase activity (GO:0003857)
ether hydrolase activity (GO:0016803)

-log10P

Reactome pathways

Up-regulated in Wound_Healing_Immune_C1_
*Extracellular matrix organization Homo sapiens R-HSA-1474244
*Collagen formation Homo sapiens R-HSA-1474290
*Elastic fibre formation Homo sapiens R-HSA-1566948
*Collagen biosynthesis and modifying enzymes Homo sapiens R-HSA-
*Assembly of collagen fibrils and other multimeric structures Homo
*Molecules associated with elastic fibres Homo sapiens R-HSA-2129
*Hemostasis Homo sapiens R-HSA-109582
*Platelet activation, signaling and aggregation Homo sapiens R-HSA-
*Axon guidance Homo sapiens R-HSA-422475
*Platelet degranulation Homo sapiens R-HSA-114608
*Developmental Biology Homo sapiens R-HSA-1266738
*Response to elevated platelet cytosolic Ca2+ Homo sapiens R-HSA-
*Cell surface interactions at the vascular wall Homo sapiens R-HSA-
*ECM proteoglycans Homo sapiens R-HSA-3000178
*Scavenging by Class A Receptors Homo sapiens R-HSA-3000480

-log10P

Down-regulated in Wound_Healing_Immune_C1
*Respiratory electron transport, ATP synthesis by chemiosmotic cou
*The citric acid (TCA) cycle and respiratory electron transport Homo
*Metabolism Homo sapiens R-HSA-1430728
*Respiratory electron transport Homo sapiens R-HSA-611105
*Mitochondrial translation initiation Homo sapiens R-HSA-5368286
*Mitochondrial translation termination Homo sapiens R-HSA-541927
*Mitochondrial translation elongation Homo sapiens R-HSA-5389840
*Mitochondrial translation Homo sapiens R-HSA-5368287
*Formation of ATP by chemiosmotic coupling Homo sapiens R-HSA-
*Complex I biogenesis Homo sapiens R-HSA-6799198
*Beta oxidation of hexanoyl-CoA to butanoyl-CoA Homo sapiens R-H
*Organelle biogenesis and maintenance Homo sapiens R-HSA-18522
*mitochondrial fatty acid beta-oxidation of saturated fatty acids Hor
*Mitochondrial Fatty Acid Beta-Oxidation Homo sapiens R-HSA-7728
*Metabolism of lipids and lipoproteins Homo sapiens R-HSA-556833

-log10P

Biological Processes

Up-regulated in Wound_Healing_Immune_C1_
*extracellular matrix organization (GO:0030198)
*collagen fibril organization (GO:0030199)
*regulation of cell migration (GO:0030334)
*protein complex subunit organization (GO:0071822)
*positive regulation of epithelial to mesenchymal transition (GO:001
*regulation of epithelial to mesenchymal transition (GO:0010717)
*cellular response to cytokine stimulus (GO:0071345)
*regulation of protein phosphorylation (GO:0001932)
*leukocyte aggregation (GO:0070486)
*eye morphogenesis (GO:0048592)
*positive regulation of cellular process (GO:0048522)
*skin development (GO:0043588)
*positive regulation of protein phosphorylation (GO:0001934)
*regulation of cell proliferation (GO:0042127)
*regulation of macrophage cytokine production (GO:0010935)

-log10P

Down-regulated in Wound_Healing_Immune_C1_
*respiratory electron transport chain (GO:0022904)
*mitochondrial ATP synthesis coupled electron transport (GO:00427
*mitochondrial translational elongation (GO:0070125)
*mitochondrial translational termination (GO:0070126)
*translational termination (GO:0006415)
*translational elongation (GO:0006414)
*mitochondrial translation (GO:0032543)
*cristae formation (GO:0042407)
*purine ribonucleoside triphosphate biosynthetic process (GO:0009
*mitochondrial ATP synthesis coupled proton transport (GO:0042776
*mitochondrial transport (GO:0006839)
*ATP biosynthetic process (GO:0006754)
*ATP metabolic process (GO:0046034)
*mitochondrial respiratory chain complex assembly (GO:0033108)
*mitochondrial electron transport, NADH to ubiquinone (GO:000612

-log10P

KEGG Pathways

Up-regulated in Wound_Healing_Immune_C1_
*AGE-RAGE signaling pathway in diabetic complications
*Protein digestion and absorption
*Axon guidance
*Proteoglycans in cancer
*Osteoclast differentiation
*ECM-receptor interaction
*Pathways in cancer
*TNF signaling pathway
*PI3K-Akt signaling pathway
*Amoebiasis
*Complement and coagulation cascades
*C-type lectin receptor signaling pathway
*Malaria
*IL-17 signaling pathway
*Transcriptional misregulation in cancer

-log10P

Down-regulated in Wound_Healing_Immune_C1_
*Non-alcoholic fatty liver disease (NAFLD)
*Parkinson disease
*Oxidative phosphorylation
*Alzheimer disease
*Huntington disease
*Thermogenesis
*Peroxisome
*Retrograde endocannabinoid signaling
*Valine, leucine and isoleucine degradation
*Citrate cycle (TCA cycle)
*Terpenoid backbone biosynthesis
*Pyruvate metabolism
*Cardiac muscle contraction
*Fatty acid degradation
*Glycine, serine and threonine metabolism

-log10P

S2D

Immunological Subtypes	Sample size
IFN-γ dominant (C2)	2
Inflammatory (C3)	17

Down-regulated in IFN_gamma_Dominant_Immune_C2_ / Up-regulated in IFN_gamma_Dominant_Immune_C2_

Gene symbol	logFC	AveExpr	t	P.Value
CCM2	1.031555	5.767136	2.317519	3.08E-02
PAQR6	-1.93451	3.191659	-2.32825	3.01E-02
PGRMC1	-1.08375	6.999647	-2.33136	2.99E-02
PAQR5	-3.83949	5.661036	-2.91322	8.40E-03

Molecular Functions

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *non-membrane spanning protein tyrosine kinase activity (GO:0004
- *MHC protein complex binding (GO:0023023)
- *GTPase regulator activity (GO:0030695)
- *MHC class II protein complex binding (GO:0023026)
- *GTPase activator activity (GO:0005096)
- *phosphatidylinositol-3,4-bisphosphate binding (GO:0043325)
- *superoxide-generating NADPH oxidase activator activity (GO:0016
- *SH3 domain binding (GO:0017124)
- *actin binding (GO:0003779)
- *cytokine receptor activity (GO:0004896)
- *MHC protein binding (GO:0042287)
- *small GTPase binding (GO:0031267)
- *T cell receptor binding (GO:0042608)
- *phosphatidylinositol 3-kinase activity (GO:0035004)
- *C-C chemokine binding (GO:0019957)

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *protein binding involved in heterotypic cell-cell adhesion (GO:0086
- *cadherin binding (GO:0045296)
- *Rho guanyl-nucleotide exchange factor activity (GO:0005089)
- *actin binding (GO:0003779)
- *ankyrin binding (GO:0030506)
- *actin filament binding (GO:0051015)
- *platelet-derived growth factor receptor binding (GO:0005161)
- *Rac guanyl-nucleotide exchange factor activity (GO:0030676)
- *sodium ion transmembrane transporter activity (GO:0015081)
- *cadherin binding involved in cell-cell adhesion (GO:0098641)
- *protein binding involved in cell-cell adhesion (GO:0098632)
- protein homodimerization activity (GO:0042803)
- potassium ion binding (GO:0030955)
- phosphate ion transmembrane transporter activity (GO:0015114)
- nucleoside-diphosphatase activity (GO:0017110)

Reactome pathways

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *Immune System Homo sapiens R-HSA-168256
- *Adaptive Immune System Homo sapiens R-HSA-1280218
- *Cytokine Signaling in Immune system Homo sapiens R-HSA-12802
- *Immunoregulatory interactions between a Lymphoid and a non-Lym
- *Interferon gamma signaling Homo sapiens R-HSA-877300
- *Costimulation by the CD28 family Homo sapiens R-HSA-388841
- *Antigen activates B Cell Receptor (BCR) leading to generation of se
- *Interferon Signaling Homo sapiens R-HSA-913531
- *Rho GTPase cycle Homo sapiens R-HSA-194840
- *Innate Immune System Homo sapiens R-HSA-168249
- *Generation of second messenger molecules Homo sapiens R-HSA-2
- *Endosomal/Vacuolar pathway Homo sapiens R-HSA-1236977
- *Signaling by Interleukins Homo sapiens R-HSA-449147
- *Signaling by Rho GTPases Homo sapiens R-HSA-194315
- *Antigen Presentation: Folding, assembly and peptide loading of clas

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *Cell-cell junction organization Homo sapiens R-HSA-421270
- *Cell junction organization Homo sapiens R-HSA-446728
- *Tight junction interactions Homo sapiens R-HSA-420029
- *Regulation of beta-cell development Homo sapiens R-HSA-186712
- *Cell-Cell communication Homo sapiens R-HSA-1500931
- *Non-integrin membrane-ECM interactions Homo sapiens R-HSA-300
- *Extracellular matrix organization Homo sapiens R-HSA-1474244
- *Developmental Biology Homo sapiens R-HSA-1266738
- *Regulation of gene expression in beta cells Homo sapiens R-HSA-2
- *Apoptotic cleavage of cell adhesion proteins Homo sapiens R-HSA-
- *IRS activation Homo sapiens R-HSA-74713
- *Apoptotic execution phase Homo sapiens R-HSA-75153
- *Metabolism of fat-soluble vitamins Homo sapiens R-HSA-6806667
- *Amyloid fiber formation Homo sapiens R-HSA-977225
- *Elastic fibre formation Homo sapiens R-HSA-1566948

Biological Processes

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *cytokine-mediated signaling pathway (GO:0019221)
- *regulation of immune response (GO:0050776)
- *interferon-gamma-mediated signaling pathway (GO:0060333)
- *cellular response to interferon-gamma (GO:0071346)
- *positive regulation of lymphocyte proliferation (GO:0050671)
- *positive regulation of T cell proliferation (GO:0042102)
- *regulation of T cell proliferation (GO:0042129)
- *T cell activation (GO:0042110)
- *negative regulation of T cell activation (GO:0050868)
- *peptidyl-tyrosine autophosphorylation (GO:0038083)
- *positive regulation of T cell activation (GO:0050870)
- *lymphocyte differentiation (GO:0030098)
- *regulation of small GTPase mediated signal transduction (GO:0051
- *regulation of B cell receptor signaling pathway (GO:0050855)
- *antigen receptor-mediated signaling pathway (GO:0050851)

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *cell-cell junction organization (GO:0045216)
- *cardiac muscle cell-cardiac muscle cell adhesion (GO:0086042)
- *macromolecular complex assembly (GO:0065003)
- *cell-cell adhesion via plasma-membrane adhesion molecules (GO:0
- *positive regulation of mesenchymal cell proliferation (GO:0002053
- *cell-cell junction assembly (GO:0007043)
- *regulation of cell proliferation (GO:0042127)
- *bicellular tight junction assembly (GO:0070830)
- *bundle of His cell-Purkinje myocyte adhesion involved in cell comm
- *actin filament organization (GO:0007015)
- *regulation of wound healing (GO:0061041)
- *apical junction assembly (GO:0043297)
- *actin filament bundle organization (GO:0061572)
- *regulation of cardiac muscle cell action potential (GO:0098901)
- *bundle of His cell to Purkinje myocyte communication (GO:008606

KEGG Pathways

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *Cell adhesion molecules (CAMs)
- *Intestinal immune network for IgA production
- *Epstein-Barr virus infection
- *Graft-versus-host disease
- *Type I diabetes mellitus
- *Antigen processing and presentation
- *Allograft rejection
- *Viral myocarditis
- *Hematopoietic cell lineage
- *Primary immunodeficiency
- *Autoimmune thyroid disease
- *Chemokine signaling pathway
- *B cell receptor signaling pathway
- *Natural killer cell mediated cytotoxicity
- *Th17 cell differentiation

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *Maturity onset diabetes of the young
- *Tight junction
- *Cell adhesion molecules (CAMs)
- *Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- *Bile secretion
- *PI3K-Akt signaling pathway
- *Tyrosine metabolism
- *Rap1 signaling pathway
- *Adherens junction
- *Proximal tubule bicarbonate reclamation
- *Complement and coagulation cascades
- *ECM-receptor interaction
- *Focal adhesion
- *Carbohydrate digestion and absorption
- *Cortisol synthesis and secretion

S2E

Immunological Subtypes	Sample size
IFN-γ dominant (C2)	2
Lymphocyte depleted (C4)	8

Down-regulated in IFN_gamma_Dominant_Immune_C2_ Up-regulated in IFN_gamma_Dominant_Immune_C2_

Gene symbol	logFC	AveExpr	t	P.Value
PGRMC1	-1.49332	7.052058	-2.27509	4.27E-02
PAQR6	-2.11244	2.960783	-2.41878	3.30E-02

Molecular Functions

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *cytokine receptor activity (GO:0004896)
- *non-membrane spanning protein tyrosine kinase activity (GO:0004
- *MHC protein complex binding (GO:0023023)
- *MHC class II protein complex binding (GO:0023026)
- *chemokine receptor activity (GO:0004950)
- *MHC protein binding (GO:0042287)
- *phosphatidylinositol-3,4-bisphosphate binding (GO:0043325)
- *chemokine activity (GO:0008009)
- *MHC class II receptor activity (GO:0032395)
- *chemokine receptor binding (GO:0042379)
- *CCR chemokine receptor binding (GO:0048020)
- *protein tyrosine kinase activity (GO:0004713)
- *MHC class II protein binding (GO:0042289)
- *T cell receptor binding (GO:0042608)
- *GTPase regulator activity (GO:0030695)

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *peptide disulfide oxidoreductase activity (GO:0015037)
- *cadherin binding (GO:0045296)
- *oxidoreductase activity, acting on the CH-OH group of donors, NAD
- *disulfide oxidoreductase activity (GO:0015036)
- *vascular endothelial growth factor receptor 2 binding (GO:0043184
- *Rho guanyl-nucleotide exchange factor activity (GO:0005089)
- *cadherin binding involved in cell-cell adhesion (GO:0098641)
- *vascular endothelial growth factor receptor binding (GO:0005172)
- *intramolecular oxidoreductase activity, transposing S-S bonds (GO
- *protein disulfide isomerase activity (GO:0003756)
- *sodium:phosphate symporter activity (GO:0005436)
- *protein binding involved in cell-cell adhesion (GO:0098632)
- *sodium ion transmembrane transporter activity (GO:0015081)
- phosphate ion transmembrane transporter activity (GO:0015114)
- anion:cation symporter activity (GO:0015296)

Reactome pathways

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *Immune System Homo sapiens R-HSA-168256
- *Adaptive Immune System Homo sapiens R-HSA-1280218
- *Immunoregulatory interactions between a Lymphoid and a non-Lyi
- *Generation of second messenger molecules Homo sapiens R-HSA-2
- *Translocation of ZAP-70 to Immunological synapse Homo sapiens R
- *Chemokine receptors bind chemokines Homo sapiens R-HSA-38010
- *Phosphorylation of CD3 and TCR zeta chains Homo sapiens R-HSA-2
- *PD-1 signaling Homo sapiens R-HSA-389948
- *Costimulation by the CD28 family Homo sapiens R-HSA-388841
- *Cytokine Signaling in Immune system Homo sapiens R-HSA-12802!
- *Class A/1 (Rhodopsin-like receptors) Homo sapiens R-HSA-373076
- *TCR signaling Homo sapiens R-HSA-202403
- *Innate Immune System Homo sapiens R-HSA-168249
- *GPVI-mediated activation cascade Homo sapiens R-HSA-114604
- *G alpha (i) signalling events Homo sapiens R-HSA-418594

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *Unfolded Protein Response (UPR) Homo sapiens R-HSA-381119
- *Metabolism of proteins Homo sapiens R-HSA-392499
- *Amyloid fiber formation Homo sapiens R-HSA-977225
- *Metabolism Homo sapiens R-HSA-1430728
- *ATF6-alpha activates chaperones Homo sapiens R-HSA-381033
- *Tight junction interactions Homo sapiens R-HSA-420029
- *RNA Polymerase I Promoter Opening Homo sapiens R-HSA-73728
- *IRE1alpha activates chaperones Homo sapiens R-HSA-381070
- *Packaging Of Telomere Ends Homo sapiens R-HSA-171306
- *DNA methylation Homo sapiens R-HSA-5334118
- *DNA Damage/Telomere Stress Induced Senescence Homo sapiens
- *Activated PKN1 stimulates transcription of AR (androgen receptor)
- *Cell-cell junction organization Homo sapiens R-HSA-421270
- *SIRT1 negatively regulates rRNA Expression Homo sapiens R-HSA-
- *XBP1(S) activates chaperone genes Homo sapiens R-HSA-381038

Biological Processes

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *T cell activation (GO:0042110)
- *positive regulation of lymphocyte proliferation (GO:0050671)
- *regulation of immune response (GO:0050776)
- *antigen receptor-mediated signaling pathway (GO:0050851)
- *cytokine-mediated signaling pathway (GO:0019221)
- *positive regulation of T cell activation (GO:0050870)
- *regulation of T cell proliferation (GO:0042129)
- *inflammatory response (GO:0006954)
- *cellular response to cytokine stimulus (GO:0071345)
- *positive regulation of T cell proliferation (GO:0042102)
- *B cell activation (GO:0042113)
- *lymphocyte differentiation (GO:0030098)
- *T cell receptor signaling pathway (GO:0050852)
- *enzyme linked receptor protein signaling pathway (GO:0007167)
- *cellular response to interferon-gamma (GO:0071346)

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *ATF6-mediated unfolded protein response (GO:0036500)
- *response to endoplasmic reticulum stress (GO:0034976)
- *actin filament bundle assembly (GO:0051017)
- *regulation of actin filament polymerization (GO:0030833)
- *IRE1-mediated unfolded protein response (GO:0036498)
- *innate immune response in mucosa (GO:0002227)
- *cellular protein metabolic process (GO:0044267)
- *calcium-independent cell-cell adhesion via plasma membrane cell-a
- *diterpenoid metabolic process (GO:0016101)
- *antibacterial humoral response (GO:0019731)
- *actin filament bundle organization (GO:0061572)
- *mucosal immune response (GO:0002385)
- *amyloid-beta metabolic process (GO:0050435)
- *negative regulation of epithelial to mesenchymal transition (GO:00
- *Rho protein signal transduction (GO:0007266)

KEGG Pathways

Up-regulated in IFN_gamma_Dominant_Immune_C2_
- *Hematopoietic cell lineage
- *Th17 cell differentiation
- *Th1 and Th2 cell differentiation
- *Chemokine signaling pathway
- *Cell adhesion molecules (CAMs)
- *Cytokine-cytokine receptor interaction
- *Primary immunodeficiency
- *Intestinal immune network for IgA production
- *Inflammatory bowel disease (IBD)
- *Leishmaniasis
- *Allograft rejection
- *T cell receptor signaling pathway
- *Graft-versus-host disease
- *Natural killer cell mediated cytotoxicity
- *Tuberculosis

Down-regulated in IFN_gamma_Dominant_Immune_C2_
- *Protein processing in endoplasmic reticulum
- *Maturity onset diabetes of the young
- *Thyroid hormone synthesis
- *Valine, leucine and isoleucine degradation
- *Tight junction
- Pyruvate metabolism
- Fatty acid degradation
- Insulin resistance
- Systemic lupus erythematosus
- Arginine and proline metabolism
- Other glycan degradation
- Bacterial invasion of epithelial cells
- Cell adhesion molecules (CAMs)
- Tyrosine metabolism
- Non-alcoholic fatty liver disease (NAFLD)

S2F

Immunological Subtypes	Sample size
Inflammatory (C3)	17
Lymphocyte depleted (C4)	8

Molecular Functions

Up-regulated in Inflammatory_Immune_C3_
- *actinin binding (GO:0042805)
- *GTPase activator activity (GO:0005096)
- *GTPase regulator activity (GO:0030695)
- semaphorin receptor binding (GO:0030215)
- neuropilin binding (GO:0038191)
- prostaglandin receptor activity (GO:0004955)
- growth factor activity (GO:0008083)
- syntaxin binding (GO:0019905)
- protein tyrosine kinase activity (GO:0004713)
- transmembrane receptor protein tyrosine kinase activity (GO:0004714)
- non-membrane spanning protein tyrosine kinase activity (GO:0004715)
- alpha-actinin binding (GO:0051393)
- cytokine activity (GO:0005125)
- prostaglandin E receptor activity (GO:0004957)
- transforming growth factor beta-activated receptor activity (GO:0005024)

Down-regulated in Inflammatory_Immune_C3_
- *disulfide oxidoreductase activity (GO:0015036)
- *peptide disulfide oxidoreductase activity (GO:0015037)
- *intramolecular oxidoreductase activity, transposing S-S bonds (GO:
- *protein disulfide isomerase activity (GO:0003756)
- *proton-transporting ATP synthase activity, rotational mechanism (
- *cadherin binding (GO:0045296)
- *protein transmembrane transporter activity (GO:0008320)
- *cation-transporting ATPase activity (GO:0019829)
- *oxidoreductase activity, acting on a sulfur group of donors, NAD(P)
- *hydro-lyase activity (GO:0016836)
- *ATP transmembrane transporter activity (GO:0005347)
- *ADP transmembrane transporter activity (GO:0015217)
- *translation initiation factor activity (GO:0003743)
- *protein channel activity (GO:0015266)
- *prenyltransferase activity (GO:0004659)

Reactome pathways

Up-regulated in Inflammatory_Immune_C3_
- *Molecules associated with elastic fibres Homo sapiens R-HSA-2129
- *Semaphorin interactions Homo sapiens R-HSA-373755
- *Eicosanoid ligand-binding receptors Homo sapiens R-HSA-391903
- *Signaling by NOTCH1 Homo sapiens R-HSA-1980143
- *Defective CHST6 causes MCDC1 Homo sapiens R-HSA-3656225
- *Defective ST3GAL3 causes MCT12 and EIEE15 Homo sapiens R-HSA-
- *Defective B4GALT1 causes B4GALT1-CDG (CDG-2d) Homo sapiens R
- *Elastic fibre formation Homo sapiens R-HSA-1566948
- *CRMPs in Sema3A signaling Homo sapiens R-HSA-399956
- *Signaling by NOTCH Homo sapiens R-HSA-157118
- *NOTCH1 Intracellular Domain Regulates Transcription Homo sapien
- *Prostanoid ligand receptors Homo sapiens R-HSA-391908
- *Diseases of glycosylation Homo sapiens R-HSA-3781865
- *Ion homeostasis Homo sapiens R-HSA-5578775
- *Ion transport by P-type ATPases Homo sapiens R-HSA-936837

Down-regulated in Inflammatory_Immune_C3_
- *Metabolism Homo sapiens R-HSA-1430728
- *The citric acid (TCA) cycle and respiratory electron transport Homo
- *Metabolism of proteins Homo sapiens R-HSA-392499
- *Asparagine N-linked glycosylation Homo sapiens R-HSA-446203
- *ER-Phagosome pathway Homo sapiens R-HSA-1236974
- *Antigen Presentation: Folding, assembly and peptide loading of clas
- *Antigen processing-Cross presentation Homo sapiens R-HSA-12369
- *Respiratory electron transport, ATP synthesis by chemiosmotic cou
- *Post-translational protein modification Homo sapiens R-HSA-59759
- *Interferon alpha/beta signaling Homo sapiens R-HSA-909733
- *Mitochondrial translation termination Homo sapiens R-HSA-541927
- *Unfolded Protein Response (UPR) Homo sapiens R-HSA-381119
- *Gluconeogenesis Homo sapiens R-HSA-70263
- *Mitochondrial translation Homo sapiens R-HSA-5368287
- *Membrane Trafficking Homo sapiens R-HSA-199991

Gene symbol	logFC	AveExpr	t	P.Value
CCM3	-0.56277	4.842558	-2.64929	**1.34E-02**

Biological Processes

Up-regulated in Inflammatory_Immune_C3_
- *regulation of release of sequestered calcium ion into cytosol by sar
- *cardiac epithelial to mesenchymal transition (GO:0060317)
- *regulation of cardiac muscle cell contraction (GO:0086004)
- *regulation of cardiac muscle contraction by regulation of the releas
- *regulation of Notch signaling pathway (GO:0008593)
- *regulation of catenin import into nucleus (GO:0035412)
- *regulation of blood coagulation (GO:0030193)
- *negative regulation of signal transduction (GO:0009968)
- *regulation of cardiac muscle contraction by calcium ion signaling (
- *regulation of cell communication by electrical coupling (GO:001064
- *regulation of axon extension involved in axon guidance (GO:00488
- *negative regulation of axon extension (GO:0030517)
- *regulation of cardiac conduction (GO:1903779)
- *regulation of relaxation of cardiac muscle (GO:1901897)
- *regulation of ryanodine-sensitive calcium-release channel activity (

Down-regulated in Inflammatory_Immune_C3_
- *mitochondrial transport (GO:0006839)
- *antigen processing and presentation of exogenous peptide antigen
- *antigen processing and presentation of peptide antigen via MHC cla
- *antigen processing and presentation of exogenous peptide antigen
- *mitochondrial ATP synthesis coupled electron transport (GO:00427
- *mitochondrial translational termination (GO:0070126)
- *cellular response to type I interferon (GO:0071357)
- *type I interferon signaling pathway (GO:0060337)
- *cristae formation (GO:0042407)
- *inner mitochondrial membrane organization (GO:0007007)
- *IRE1-mediated unfolded protein response (GO:0036498)
- *translational termination (GO:0006415)
- *Golgi vesicle transport (GO:0048193)
- *purine ribonucleoside monophosphate biosynthetic process (GO:00
- *mitochondrial translational elongation (GO:0070125)

KEGG Pathways

Up-regulated in Inflammatory_Immune_C3_
- Pathways in cancer
- Renin secretion
- Th1 and Th2 cell differentiation
- Taurine and hypotaurine metabolism
- AGE-RAGE signaling pathway in diabetic complications
- Th17 cell differentiation
- Axon guidance
- TNF signaling pathway
- Notch signaling pathway
- Nitrogen metabolism
- Breast cancer
- cAMP signaling pathway
- Wnt signaling pathway
- Proximal tubule bicarbonate reclamation
- Hippo signaling pathway

Down-regulated in Inflammatory_Immune_C3_
- *Protein processing in endoplasmic reticulum
- *Citrate cycle (TCA cycle)
- *Non-alcoholic fatty liver disease (NAFLD)
- *Parkinson disease
- *Amino sugar and nucleotide sugar metabolism
- *Antigen processing and presentation
- *Epstein-Barr virus infection
- *Oxidative phosphorylation
- *Huntington disease
- *Protein export
- *Thermogenesis
- *Human immunodeficiency virus 1 infection
- *Alzheimer disease
- *Glycolysis / Gluconeogenesis
- *Proteasome

CCA

S3A.

**D-1.** **HCC**

D-2. **CCA**

E-1.

E-2.

S4A.

Normal liver tissue (NORM)

Hepatocellular Carcinoma (HCC)

Cholangiocarcinoma (CCA)
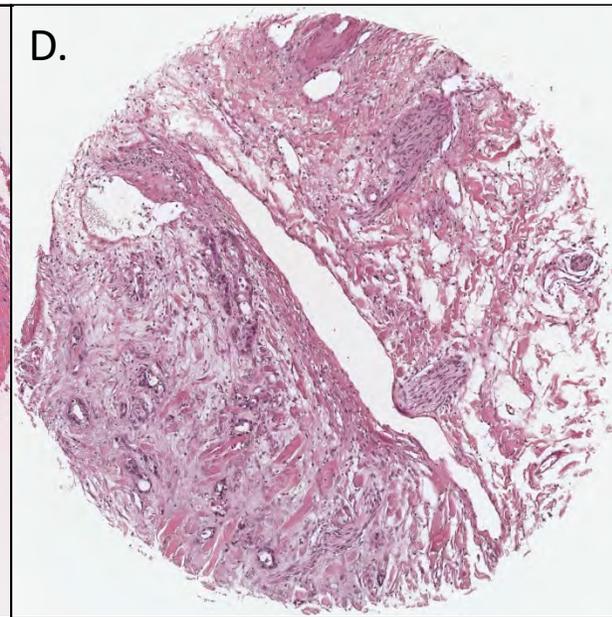
Hepatocholangiocarcinoma (cHCC-CCA)
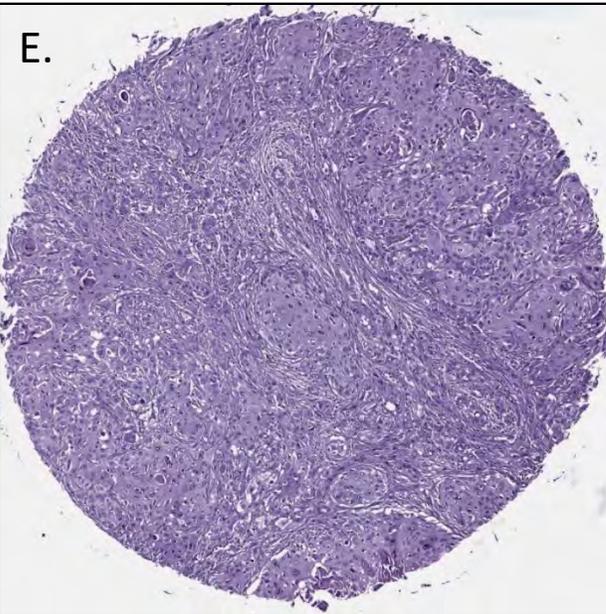
Adenosquamous Carcinoma (ASC)
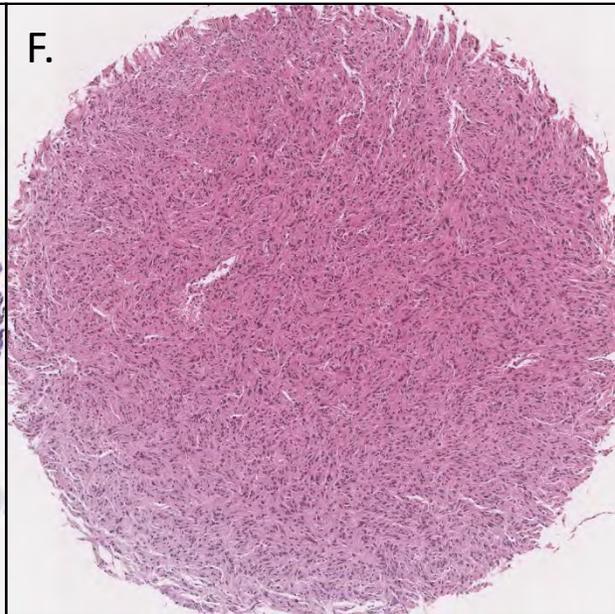
Undifferentiated Pleomorphic Sarcoma (UPS)
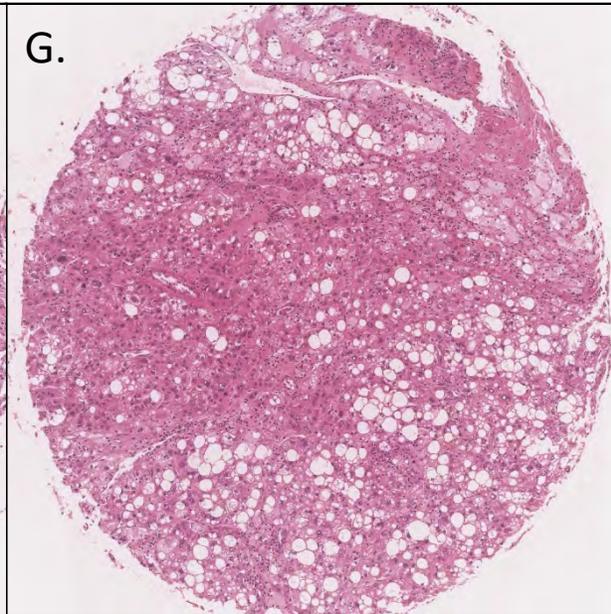
Clear Cell Carcinoma (CCC)

Hepatic Angiosarcoma (HAS)

S5A. 20X

	DAPI	AFP	MERGE
NORM			
CCA			
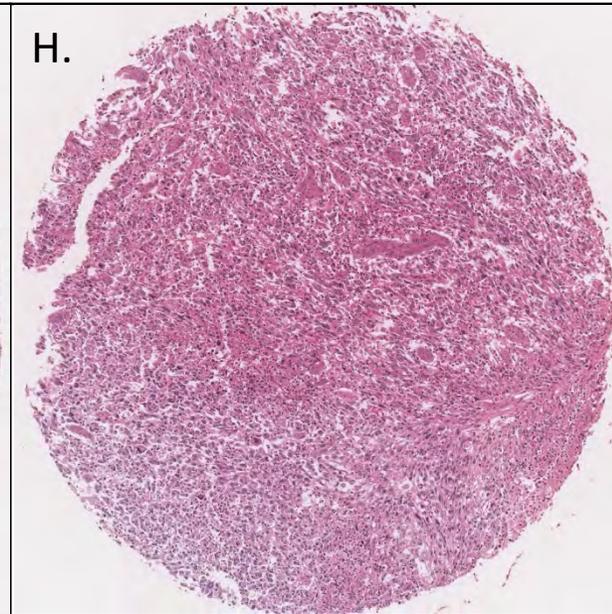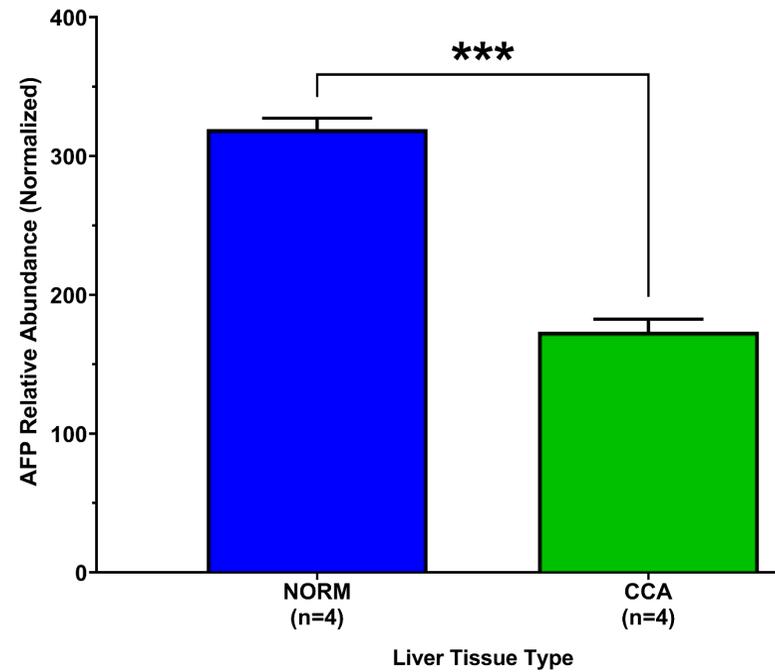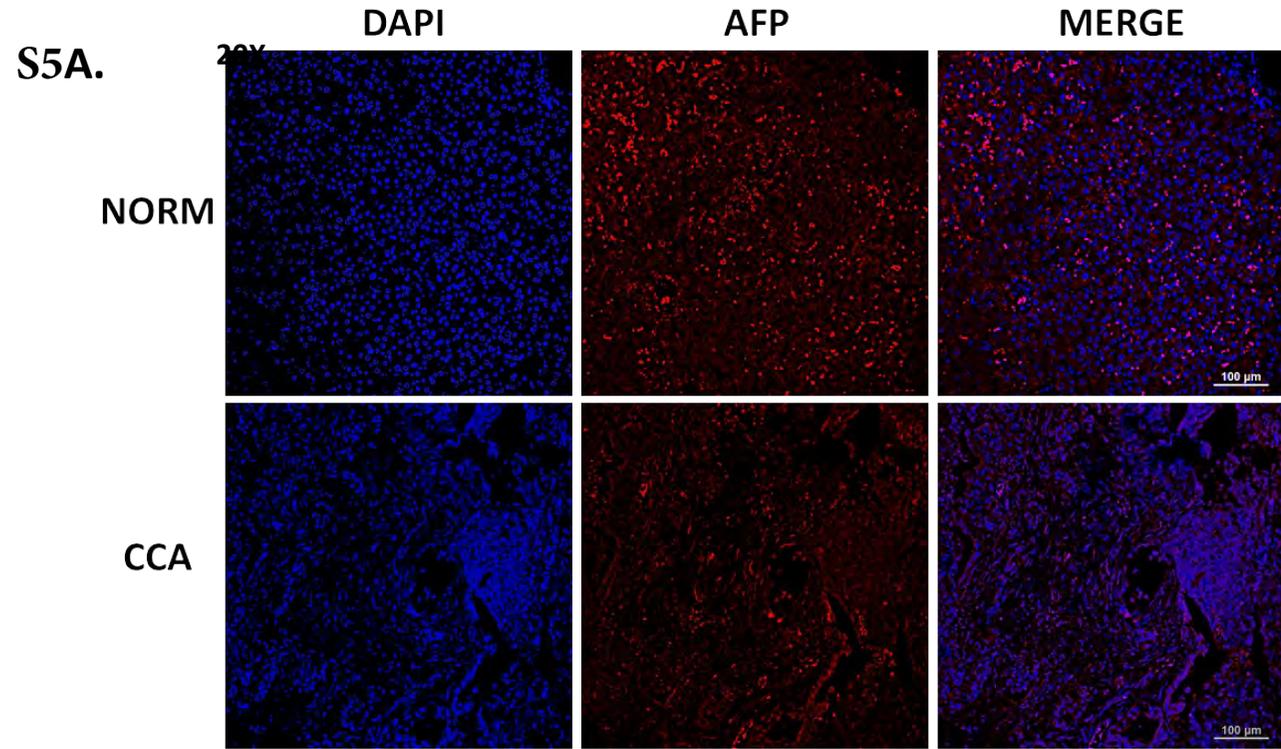
B.

nPRs Quantification Summary

Cancer Subtype Comparisons					
	HCC	**CCA**	**CCC**	**UPS**	**HAS**
HCC		***	***	***	***
CCA	***		N.S.	N.S.	N.S.
CCC	***	N.S.		N.S.	N.S.
UPS	***	N.S.	N.S.		N.S.
HAS	***	N.S.	N.S.	N.S.	